ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 45, NO. 4



OCTOBER, 1956

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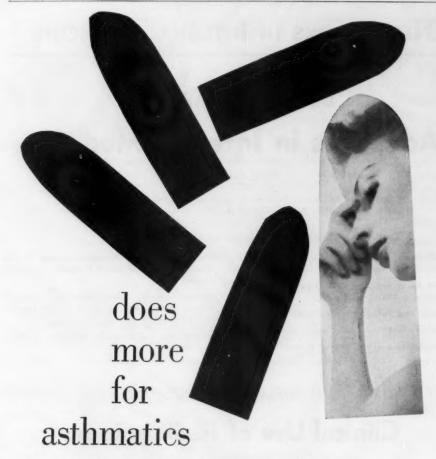
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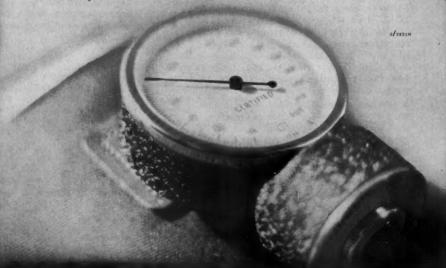
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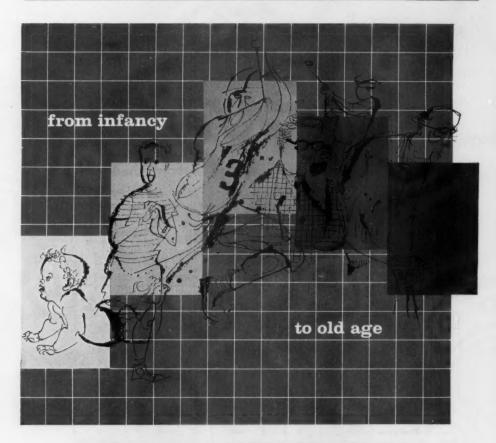
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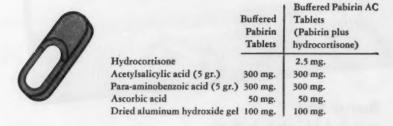
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disappointments and responsibilities.

to help the depressed and anxiety-ridden housewife who is surrounded by a monotonous routine of daily problems, disappointments and responsibilities.

With 'Dexamyl' you can often help her to face her problems; help her to regain lost interests; help her to rediscover the zest and purpose in life. The normalizing effect of 'Dexamyl' is free of the dullness caused by many "anti-anxiety" agents alone; free of the excitation sometimes caused by stimulants alone. Her mood normalized, the disturbing mental and physical symptoms often vanish.

DEXAMYL* tablets • elixir • Spansule† capsules

smoothly and subtly relieves both anxiety and depression

Each 'Dexamyl' Tablet or teaspoonful (5 cc.) of the Elixir contains Dexedrine* (dextro-amphetamine sulfate, S.K.F.), 5 mg., and amobarbital, ½ gr.

Each 'Dexamyl' Spansule No. 1 gradually releases the equivalent of two tablets; each 'Dexamyl' Spansule No. 2-the standard strength-gradually releases the equivalent of three tablets.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

Patent Applied For.

Hypertensive symptoms relieved in 96% of patients

"Comparison of pentolinium [Ansolysen] with other preparations in 25 patients with severe essential hypertension, for whom all other methods of management had failed, showed that pentolinium is the most effective of available agents in reducing dangerously high blood pressure to the desired levels, and in modifying some of the complications of hypertension, as cardiac decompensation, cardiomegaly and retinopathy....

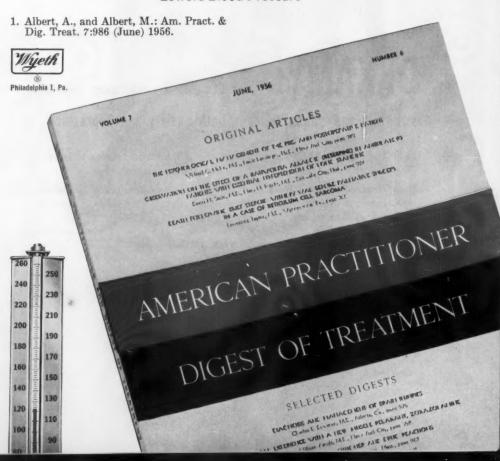
"In 96 per cent (24 patients) clinical symptoms were relieved and the blood pressure maintained at comfortable levels..."

ANSOLYSEN

TARTRATE

Pentolinium Tartrate

Lowers Blood Pressure





HOFFMANN-LAROCHE INC.

PHARMACEUTICALS AND VITAMINS . NUTLEY 10 . NEW JERSEY . NUTLEY 2-5000

From: Qublic Relations Department NEW NUtley 2-5000, Extension 731 For Immediate Release

Only two doses a day are needed in most cases when the <u>new</u> antibacterial, Lipo Gantrisin 'Roche,' is used. Recent studies indicate that Lipo Gantrisin provides adequate blood levels for at least twelve hours; this is why it usually produces a round-the-clock effect with one dose in the morning and another at night. In exceptionally severe infections, three to four doses a day may be used initially.

Lipo Gantrisin Acetyl contains Gantrisin Acetyl
in a readily absorbable vegetable oil emulsion. It
provides the same therapeutic advantages as Gantrisin
-- wide antibacterial spectrum, little likelihood of
renal blocking, no need for alkalies or forcing of
(over)

NEWS RELEASE

fluids, and an exceptionally low incidence of side effects.

Each teaspoonful of Lipo Gantrisin® Acetyl (acetyl sulfisoxazole) provides the equivalent of 1 Gm of Gantrisin -- twice the concentration of most liquid sulfonamide preparations. The small volume of each dose and the two-a-day dosage schedule are of special value in the treatment of children and elderly invalids.

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NOW...CORTICOID THERAPY OF SEVERE ASTHMA

CAN BE MADE SAFER
BY CONCURRENT THERAPY WITH

Cardalin

(protected aminophylline)

Cardalin increases vital capacity...makes it possible to reduce dosage of corticoids and thus avoid risk of side effects

instead of these risks...

- activation and perforation of gastric ulcers
- water and salt retention
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Cardalin

provides a full therapeutic dose of aminophylline orally without gastric irritation.

TO SERVE YOUR PATIENTS TODAY-

Call your pharmacist for any additional information you may need to help you prescribe Cardalin. He has been especially alerted.

these benefits with Cardalin+Corticoids

- safer control of asthma
- quicker remissions
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- less costly treatment

Each tablet contains:

Aminophylline 5.0 gr.
Aluminum hydroxide 2.5 gr.
Ethyl aminobenzoate 0.5 gr.

For Rx economy, prescribe Cardalin in 50's.

Also available—Cardalin-Phen, containing Cardalin plus ¼ gr. phenobarbital.

IRWIN, NEISLER & COMPANY . DECATUR, ILLINOIS

"a safe and reliable soporific and sedative"



(heptabarbital GEIGY)

Effective Hypnosis With ordinary hypnotic dosage of 200 mg., 90 per cent of patients achieve sleep within the hour, lasting generally throughout the night.1 Compared with other barbiturates, a notable absence of hangover or other side effects has been recorded.1-8

The therapeutic ratio of MEDOMIN is unusually wide, as demonstrated both in the laboratory' and in the clinic."

Reliable Sedation MEDOMIN calms the tense and anxious patient more effectively than phenobarbital and is "... particularly beneficial...in patients who exhibit anxiety or mild restlessness."2

> Dosage: Hypnotic: One or two 200 mg. tablets one hour before bedtime. edative: One 50 mg. or 100 mg. tablet two or three times daily.

(1) Bauer, H. G., and Reckendorf, H. K.: A Study of the Soporific and Sedative Effectiveness of a Cycloheptenyl-ethylbarbiturate, New York State J. Med., to be published. (2) Brusca, D. D.: Clinical Study of Cycloheptenyl-ethylbarbiturate (Medomin) for Insomnia, J. Nerv. & Ment. Dis. 121:67, 1955. (3) Fazekas, J. F., and Koppanyi, T.: The Effects of Cycloheptenylethyl Barbituric Acid (Medomin) in Man, to be published. (4) Koppanyi, T.; Morgan, C. F., and Princiotto, J. V.: Essential Elimination of Sodium Cycloheptenyl-ethylbarbiturate (Medomin) in Rabbits, J. Am. Pharm. A. (Scient. Ed.) 44:221, 1955.

MEDOMIN® (heptabarbital GEIGY). Scored tablets of 50 mg. (pink), 100 mg. (yellow) and 200 mg. (white).



GEIGY PHARMACEUTICALS
DIVISION OF GEIGY CHEMICAL CORPORATION 220 CHURCH STREET, NEW YORK 13, N. Y.

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Estrogen-androgen therapy effectively prevents postpartum breast engorgement

Satisfactory results were obtained in over 96 per cent of cases in a series of 267 patients who received estrogen and androgen as combined in "Premarin" with Methyltestosterone. Therapy was started as soon as possible after delivery. No untoward side effects were noted. In addition, the absence of mental depression in the puerperium was considered of notable importance.*

*Fiskio, P. W.: GP 11:70 (May) 1955.

"PREMARIN" with METHYLTESTOSTERONE

for combined estrogen-androgen therapy



Ayerst Laboratories . New York, N. Y. . Montreal, Canada



Mytelase chloride (WIN 8077) is a new antimyasthenic compound with definite advantages over older cholinergics.

More pronounced improvement

Patients "... feel better, are stronger, and are closer to their normal health."

More prolonged action

As a rule Mytelase "...has roughly twice the effectiveness per milligram of neostigmine in reducing the symptoms of myasthenia gravis, and approximately twice the duration." Some patients can replace their former 10 to 60 tablets daily with as few as 2 tablets of Mytelase; sleep need not be interrupted for dosage.

Fewer gastro-intestinal side effects

Supplied: Tablets, scored, of 10 mg. and 25 mg., bottles of 100.

 Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: J.A.M.A., 158:625, June 25, 1955.

2. Schwab, R.S.: Am. Jour. Med., 19:734, Nov., 1955.

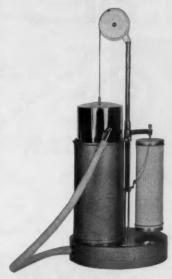
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Write for booklet discussing in detail clinical experience, dosage, side effects and precautions to be observed.

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THE COLLINS RECORDING VITALOMETER



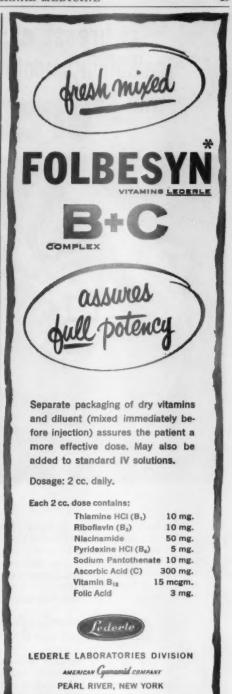
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This latest addition to the Collins' line of pulmonary function equipment consists of a 6 liter spirometer, one tube breathing system and a high speed clock mechanism that gives a paper travel of 1 cm. a second. It enables you to measure the amount exhaled in the first one half-three quarters and one second of the effort as well as the total amount and time.

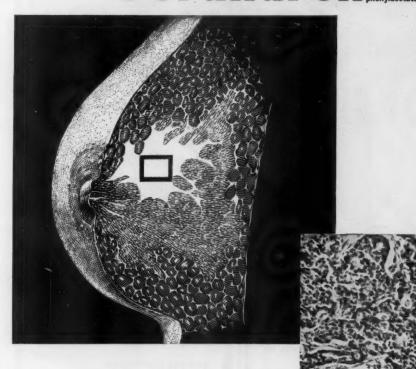
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in breast carcinoma... palliation smoothly maintained with Perandren



Androgens — in large doses — can provide palliation in advanced inoperable mammary cancer. Of all clinically used androgens, Perandren phenylacetate provides longer and stronger anabolic and androgenic effects — which are easily obtained, smoothly maintained.

One dose is usually effective for a full month

The virtually painless injection of Perandren phenylacetate spares the cancer patient much discomfort, frequency of injections, inconvenience. Treatment should be started with short-acting Perandren propionate — 150 to 300 mg. weekly. When optimal dosage has been determined, the same amount of Perandren phenylacetate can then be injected — once a month,

Perandren® phenylacetate (testosterone phenylacetate CIBA): Multiple-dose Vials, 10 ml., each ml. containing 50 mg. Perandren phenylacetate. Perandren® propionate (testosterone propionate U.S.P. CIBA): Ampuls, 1 ml., each containing 25 mg. Perandren propionate; Multiple-dose Vials, 10 ml., each ml. containing 25, 50 or 100 mg. Perandren propionate.

CIBA

SUMMIT, N. J.



FOR YEARS Thesodate, the original enteric-coated tablet of Theobromine Sodium Acetate, has been used extensively for cardiac and circulatory disorders such as coronary artery disease which is often accompanied by hypertension.

NOW COMBINED with the whole powdered root of Rauwolfia serpentina (no single alkaloid or fraction having shown the beneficial effects of the whole crude root), R-S-THESODATE offers a more ideal treatment for essential hypertension whether or not coronary artery disease is present. In most cases, its use should effect gradual but sustained blood pressure reduction and a lowered pulse rate if it has been elevated.

SYMPTOMS OF HYPERTENSION should also be alleviated by the tranquilizing effect of one of Rauwolfia's alkaloids. A sense of well-being usually occurs within a few days after starting the patient on R-S-THESODATE. Shortly after, the normotensive effect becomes more noticeable, and thus in most cases the patients will enjoy both symptomatic and systemic improvement.

R-S-THESODATE TABLETS, enteric-coated to prevent gastric distress, are taken at meals and at bedtime. The bedtime tablet prepares the patient for early morning activities.

Each enteric-coated tablet contains:

Theobromine Sodium Acetate (7½ gr.) 0.5 Gm. Rauwolfia serpentina .. . 50 mg. Supplied in 100's and 500's

BREWER & COMPANY, INC.

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CORONARY

ARTERY DISEASE

in following formulas

TABLETS THESODATE 71/2 gr. or 3% gr.

WITH PHENOBARBITAL

7½ gr. with ½ gr. 7½ gr. with ¼ gr.

3% gr. with 14 gr.

WITH POTASSIUM IODIDE 5 gr. with 2 gr.

WITH POTASSIUM IODIDE AND PHENOBARBITAL 5 gr. with 2 gr. and 1/4 gr.

> all formulas ENTERIC-COATED

Supplied in 100's and 500's

WORCESTER B. MASSACHUSETTS U.S.A.

In Angina Pectoris



the acute attack

EDIHALER-NITRO is octyl nitrite MEDIHALER NITES (1%) in aerosol solution; delivered by metered-dosage nebulization, using the lungs as portal of entry, it assures fastest relief and prolonged effect: it is free from disagreeable. irritating odor, and less apt to produce side actions than are nitroglycerin and amyl nitrite.

To be used only with the MEDI-HALER® ORAL ADAPTER made of unbreakable plastic with no moving parts. Medication and Adapter fit into pocket-size plastic carrying case. One or two inhalations provide prompt relief of an attack of angina pectoris.

MEDIHALER...The New Measured-Dose Principle of Nebulization

and for definitive therapy... fewer and fewer attacks of less and less intensity

Long-acting tablets containing pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid® (alseroxylon) 1 mg. reduce the incidence and intensity of attacks and lead to objective improvement demonstrable by ECG. Dosage: one or two tablets q.i.d., before meals and on retiring Pentoxylon^{*}

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couple had 8yr. history of infertility.

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Many clinicians and investigators have reported dramatic results with 'Cytomel' in the treatment of reproductive disorders such as:

> male and female infertility decreased libido amenorrhea dysmenorrhea premenstrual tension

Information on this interesting new drug and samples for clinical trial in your own patients are available on request.

Cytomel* 5 mcg. and 25 mcg. tablets

Smith, Kline & French Laboratories, Philadelphia 1, Pa.

*Trademark for L-triiodothyronine, S.K.F.





Superior antacid action and...

"For palatability, many patients prefer Maalox'

MAALOX®, an efficient antacid suspension of magnesiumaluminum hydroxide gel, is smooth-textured, and always pleasant to take. MAALOX was tested by thousands of hospital outpatients, who preferred it to other antacids. Indeed, high patient acceptability (without danger of constipation) is one of the outstanding advantages of MAALOX therapy.2

As to chemistry: MAALOX has more acid-binding capacity than aluminum hydroxide gel, and maintains its antacid effect twice as long.3

Supplied: Suspension, bottles of 12 fluidounces.

- Tablets, bottles of 100. Samples sent promptly on request. 1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
- 2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
- 3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

For Pain try Ascriptin Tablets (Aspirin buffered with Maalox)

- Doubles blood salicylate level
- Action more prolonged
 High gastric tolerance level
- · Clinically proved.

Samples on request

"... better suited for antacid therapy"2

WILLIAM H. RORER, Inc.



PHILADELPHIA, PA.

Announcing

'INVERSINE'

Mecamylamine Hydrochloride

An oral antihypertensive that is

TOTALLY NEW
CHEMICALLY DIFFERENT
CLINICALLY RELIABLE



The same dose provides the same results . . . day after day.

NVERSINE,' a secondary amine, is a new and extremely potent antihypertensive agent. It is totally unlike the poorly and erratically absorbed ganglionic blockers of the quaternary ammonium type and has the following clinically demonstrated properties:

1. Excellent reproducibility of effects.

2. Most potent of all available oral ganglionic blockers (10 to 20 times more potent than pentolinium and about 90 times more potent than hexamethonium).

- 3. Smooth, predictable response: In a given patient, the same dose of 'INVER-SINE' elicits the same blood pressure response, time after time, with minimal day-to-day fluctuation.
- 4. Remarkable physiologic economy resulting in long duration of action, sustained effect.
- 5. Gradual onset of effect.
- **6.** Small oral dosage produces required hypotensive effect.
- 7. Effective even in patients refractory to hexamethonium and other ganglionic blocking agents.

In all these respects, 'INVERSINE' differs greatly from all other available ganglionic blocking agents and is, in effect, in a unique category among antihypertensives.

CLINICAL STUDIES

'Inversine' has been used by many investigators on thousands of patients. In all this clinical work, this new and very potent agent has amply fulfilled its laboratory promise. By demonstrating reproducibility, high potency and smooth effectiveness with minimal fluctuation — all resulting directly from its complete absorption from the gastro-intestinal tract — 'Inversine' has successfully circumvented many of the objections to the use of ganglionic blockade in hypertension.

In the opinion of one reviewer "... the most useful ganglionic blocking agent to be introduced is mecamylamine ('Inversine').... This drug is completely absorbed when given by mouth and has such a gradual onset and offset of action that a continuous and effective level of blockade can readily be achieved..."

Further, in one of many clinical trials,† "The over-all response rate was 92%, and 24% of the patients became normotensive." Investigators have found 'Inversine' to be "... the most potent and effective of the three drugs in reducing the blood pressure..." ['INVERSINE' and two other ganglionic blocking agents.]

' Moreover, following ganglionic blockade with 'INVERSINE,' some patients with hypertension may experience relief of pre-existing headache and angina pectoris. Many patients with retinopathy, congestive heart failure and electrocardiographic abnormalities, have shown signs of improvement during treatment with 'INVERSIME.'

'Inversine' was thus shown to be most valuable in the management of hypertensive vascular disease.

SIDE EFFECTS

'INVERSINE' (mecamylamine), though comparatively nontoxic, is a very potent agent which must be used with care. Side effects observed during clinical use are due to excessive pharmacologic action. They may be minimized by careful adjustment of dosage and close supervision of the patient.

* * * * *

Judged by any standard 'Inversine' (mecamylamine) is the most satisfactory agent in the treatment of hypertension by ganglionic blockade. It is the most potent and most reliable oral agent for the management of hypertension.

References:

- 1. Sturgis, C. C., et al.: Advances in Internal Medicine, J. Michigan M. Soc. 55:154 (Feb.) 1956.
- 2. Moyer, J. H. et al.: Drug Therapy of Hypertension: Preliminary Observations on the Clinical Use of Mecamylamine (A Ganglionic Blocking Agent) in Combination with Rauwolfia for the Treatment of Hypertension, Med. Rec. & Ann. 49; 390 (Sept.) 1955.
- † In this clinical trial all patients were given, in addition to one of the ganglionic blocking agents, a constant daily amount of reserpine.

'INVERSINE' is the trademark of Merck & Co., Inc.



MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

For the Failing Heart

In Infants and Children



GITALIGIN® DROPS

Offers "greater safety margin" GITALIGIN in a pleasant tasting form

Now whenever any of your little patients require digitalis therapy, give them GITALIGIN DROPS.

GITALIGIN, White's brand of amorphous gitalin, is unique among cardioactive glycosides because its therapeutic dose is approximately only 1/3 the toxic dose. In contrast, the therapeutic dose of other glycosides is approximately 3/3 the toxic dose.1-11

Precise fractional dosage made possible with GITALIGIN DROPS is especially advantageous in the management of advanced cardiac disease when the myocardial reserve is markedly limited.

Dosage:

In children the digitalizing dose is 0.05 mg. per pound of body weight, in divided doses: one-half initially, and the remainder is given in halves at 6 to 12 hour intervals. The maintenance dose usually is 1/10 the digitalizing dose.

Available:

In 30 cc. bottles with dropper calibrated to measure 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 mg. GITALIGIN.

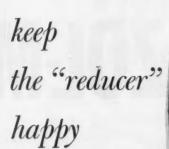
Gitaligin Tablets;

0.5 mg. scored, in bottles of 30 and 100.

- 1. Am. Heart J. 52:300 (Aug.) 1956. 2. Ann. Int. Med. 40:820 (Apr.) 1954,
- 3. Am. J. M. Sc. 227:188 (Feb.) 1954
- 4. Ann. Int. Med. 39:1189 (Dec.) 1953. 5. Am. Heart J. 45:108 (Jan.) 1953. 6. Am. Heart J. 46:276 (Aug.) 1953.
- 7. Arch. Int. Med. 90:224 (Aug.) 1952.
- 8. Circulation 5:201 (Feb.) 1952. 9. New Eng. J. Med. 246:225 (Feb.) 1952.
- 10. Am. Heart J. 42:292 (Feb.) 1951,
- 11. Fed. Proc. 9:256 (Mar.) 1950.

WHITE LABORATORIES, INC.

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'Methedrine'

'Methedrine' dispels abnormal craving for food, and subtly elevates the mood. Reducing diets are accepted easily, without frustration.

'Methedrine' is safe, in recommended doses, for pregnant women.

'Methedrine' brand Methamphetamine Hydrochloride Tablet of 5 mg., scored.

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SULFONAMIDE

THERAPY

ALDIAZOL-M

Aldiazol-M combines two of the most effective sulfonamides, sulfadiazine and sulfamerazine, with a systemic alkalizer, sodium citrate. High, prolonged blood levels are assured, while the danger of crystalluria is reduced.

Because of its inherent safety, it is often prudent to use Aldiazol-M instead of antibiotics and thus preclude the risk of sensitization.

Supplied as a suspension and as a tablet

Each teaspoonful contains:

Sulfadiazine* .						0.25	Gm.
Sulfamerazine*						0.25	Gm.
Sodium Citrata						1.00	Gm

Each tablet contains:

Sulfadiazine* .					0.125	Gm.
Sulfamerazine*					0.125	Gm.
Sodium Citrate					0.250	Gm.

*Microcrystalline

The S. E. Massengill Company

Bristol, Tennessee

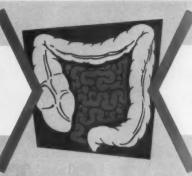
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a nutritive deconstipant

MODANE

which not only relieves but also rehabilitates

Improves peristalsis and bowel movement, suggesting a selective stimulation of the intrinsic nerve plexus—not irritation.



Acts as a laxative on the large bowel only—does not affect motor activity of the small bowel.

Actually, a therapeutic approach . . . relief plus repair for the atonic bowel.

Acts surely, gently, overnight — without griping. Non-toxic, non-habitforming

Provides Pantothenic Acid
— proven indispensable to
acetyl-choline formation
and normal bowel function.

Each tablet of MODANE contains Danthron 75 mg. and Pantothenic Acid 25 mg.... Danthron to encourage peristalsis, Pantothenic Acid for rehabilitation of the atonic bowel.

Dosage....MODANE REGULAR—one yellow tablet after the evening meal.

MODANE MILD (half strength, for hypersensitive, pregnant, pediatric and diet-restricted patients)—one pink tablet after the evening meal.

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO

WARREN-TEED

in inflammatory skin diseases



all the benefits of the "predni-steroids" plus positive antacid action to minimize gastric distress

ROUTINELY ACHIEVED WITH

Co-Deltra'

Clinical evidence^{1,2,3} indicates that to augment the therapeutic advantages of prednisone and prednisolone, antacids should be routinely co-administered to minimize gastric distress.

References: 1. Boland, E. W., J.A.M.A. 168:813, (February 25,) 1956. 2. Margolis, H. M. et al, J.A.M.A. 158:454, (June 11,) 1955. 3. Bollet, A. J. et al, J.A.M.A. 158:459, (June 11,) 1955.



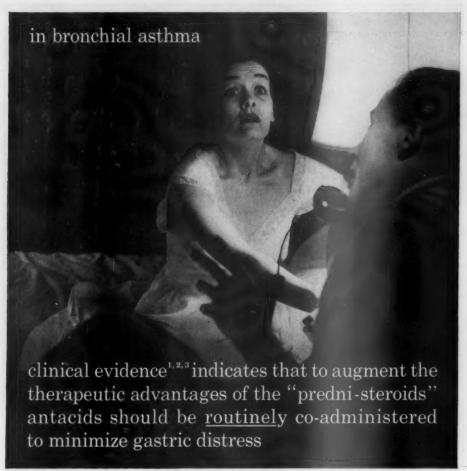
Co-Hydeltra (Buffered Prednisolone)

2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.



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ROUTINE CO-ADMINISTRATION MEANS

All the benefits of the "predni-steroids" plus positive antacid action to

minimize gastric distress.

Co-Hydeltra



2.5 mg. or 5 mg. prednisone or prednisolone with 50 mg. magnesium trisilicate and 300 mg. aluminum hydroxide gel.



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PHILADELPHIA 1. PA

References: 1. Boland, E. W., J.A.M.A. 160:613, (February 25,) 1956. 2. Margolis, H. M. et al, J.A.M.A. 158:464, (June 11,) 1955. 3. Bollet, A. J. et al, J.A.M.A. 158:459, (June 11,) 1955. 'CO-DELTRA' and 'CO-HYDELTRA' are the trademarks of MERCE & Co., INC.

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arlidin

vasorelaxation more tissue oxygen improved muscle metabolism pain relief safe • rapid • sustained

helps your peripheral vascular patients walk longer, further, in more comfort

"strong muscle vasodilator activity and an adequate increase in cardiac output"¹

"safe vasodilative agent of minimal toxicity and optimal tolerance"² in intermittent claudication diabetic vascular disease Raynaud's disease thromboangiitis obliterans ischemic ulcers night leg cramps

ARLIDIN dilates peripheral blood vessels in distressed muscles, relaxes spasm, increases both cardiac and peripheral blood flow...to send more blood where more blood is needed.

dose: 1 tablet t.i.d. or q.i.d. bottles of 50, 100 and 1000.



brand of nylidrin hydrochloride tablets 6 mg.

1. Pomeranze, J. et al.: Angiology, June, 1955 2. Freedman, L.: Angiology 6:52, Feb. 1955.

Write for samples and literature

arlington-funk laboratories division of U. S. Vitamin Corporation 250 East 43rd Street, New York 17, N.Y.

*Trade Mari



Conservative therapy in hypertension can be made more effective

EFFECTIVE: When combined with reserpine, hypotensive effects of protoveratrines A and B can be achieved with smaller dosage. Side effects are markedly reduced.

SAFE: Veralba-R can be given routinely without causing postural hypotension or impairing the blood supply to the heart, brain and other vital organs. Dosage is simple.

ACCURATE: Potency is defined by chemical assay. All ingredients are in purified, crystalline form.

Each Veralba-R tablet contains 0.4 mg. of protoveratrines and 0.08 mg. of reserpine. Bottles of 100 and 1000 scored tablets.

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three patients...three piperidols

favorite for generalized G.I. dysfunction

TRIDAL

paired piperidol action

gives rapid, prolonged relief throughout the G.I. tract



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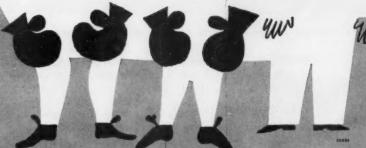


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and when peptic ulcer is the problem: cholinolytic

PIPTAL*

Normalizes motility and secretion; prolongs remissions, curbs recurrences.



Patients on TRIDAL, DACTIL or PIPTAL remain singularly free of anticholinergic-antispasmodic side effects.



New Potentiated Pain Relief

A.P. C. Demerol

Each tablet

Caffeine...... 30 mg. (½ grain) Demerol® hydrochloride...... 30 mg. (1/2 grain)

Average Adult Dose... 1 or 2 tablets repeated in three or four hours as needed.

O marked potentiation of analgesia

plus mild sedation

..... antispasmodic action

..... antipyretic action

..... no constipation

..... no interference with micturition

"Such a combination has proved clinically to be far more effective and no more toxic than equivalent doses of any of these used singly. "

Supplied in bottles of 100 tablets.

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The Thyroid Gland

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*Richardson, H.: The Thyroid and Parathyroid Glands, Philadelphia, P. Blakiston's Sons & Co., 1905, pp. 9 and 197.

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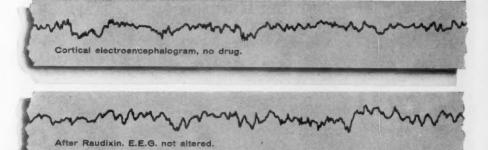


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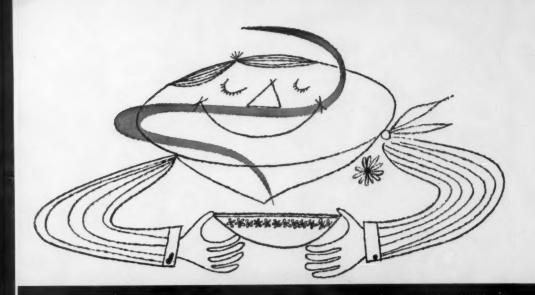
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*Ausman, D. C.: Cobalt-Iron Therapy in the Treatment of Some Common Anemias Seen in General Practice, in press.

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Course No. 1, RECENT ADVANCES IN CARDIOVASCULAR DISEASES: Mt. Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-directors.	×														
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Course No. 3, CLINICAL NEUROLOGY: Jefferson Medical College of Philadelphia, Philadelphia, Pa.; Bernard J. Alpers, M.D., F.A.C.P., Director.		×		1		1									
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Course No. 5, SELECTED PROBLEMS IN INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., Director.				1	1	ivigedne	×				smisind				1
Course No. 6, GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.	1			1		4.L		4-8)	1			1
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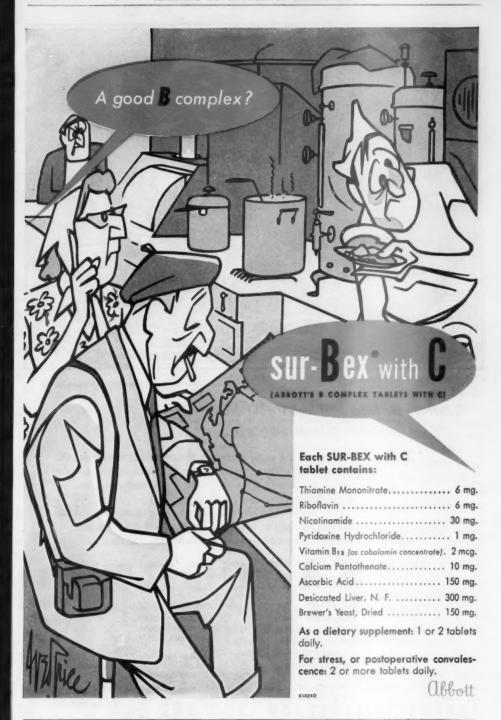
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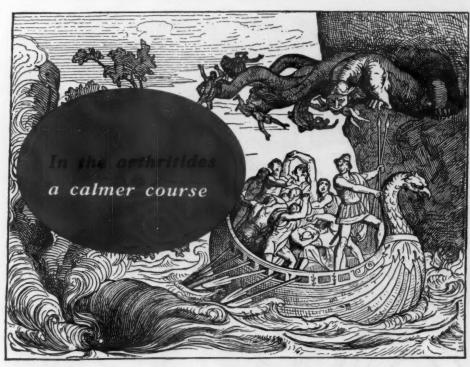
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¹Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105

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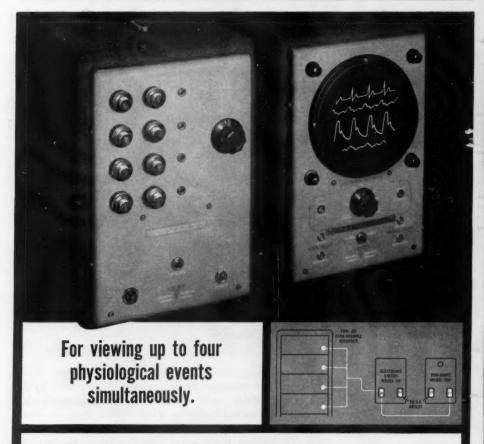
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¹Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, As a Hypotensive-Tranquilizer. J.A.M.A. 161:424 (June 2, 1956).

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Lemere, F.: Northwest Med. 54: 1098, 1955.

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Sokoloff, O.J.: A.M.A. Arch. Dermat. In press.

"Of special importance is the fact that Miltown does not appear to affect autonomic balance—which in alcoholics is often unstable . . ."

Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. 17: 19, 1956.

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Borrus, J.C.: J.A.M.A. 187: 1596, 1955.

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Selling, L.S.: J.A.M.A. 157; 1594, 1955,

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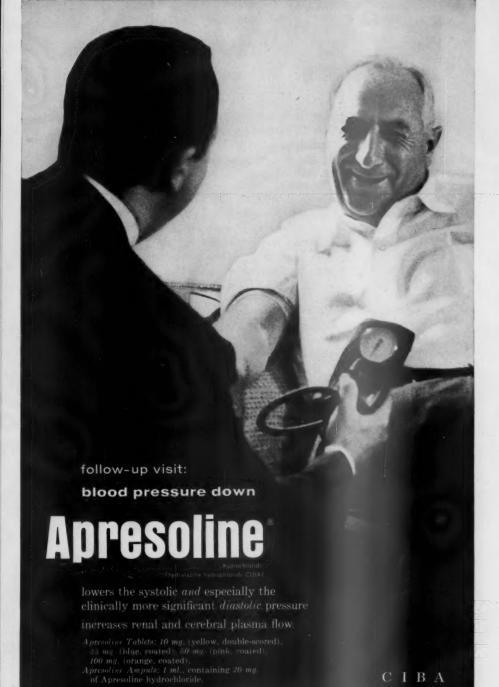


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ANNALS OF INTERNAL MEDICINE

VOLUME 45

OCTOBER, 1956

NUMBER 4

ACUTE CORONARY INSUFFICIENCY: ITS DIFFER-ENTIAL DIAGNOSIS AND TREATMENT*

By ARTHUR M. MASTER, F.A.C.P., HARRY L. JAFFE (by invitation), LEONARD E. FIELD, F.A.C.P., and EPHRAIM DONOSO (by invitation), New York, N. Y.

As the years pass, the known incidence of coronary disease continues to rise. Today, about one of every three men over the age of 35 and the vast majority of men over 50 have a significant degree of sclerosis.1-4 The incidence is much lower in women, particularly before the menopause; but coronary sclerosis in women also is more common than was previously thought.

The manifestations of coronary disease are extremely variable. In many people the disease is completely asymptomatic, probably for many years. In at least 50% of patients with definite coronary artery disease, which may even be severe, the resting electrocardiogram is normal; occasionally, the electrocardiogram shows abnormalities before clinical symptoms or signs develop. In most cases, however, the presence of coronary disease is evidenced by the appearance of angina pectoris, an episode of acute coronary insufficiency, or an acute coronary occlusion; sometimes, congestive failure or an arrhythmia, such as auricular fibrillation or heart block, is the first manifestation of the disease.

The most common symptom of coronary disease is chest pain. This complaint was encountered in over 60% of 1,000 consecutive private cardiac consultations.5 To be sure, chest pain may be caused by numerous other organic and functional conditions. Indeed, it is one of the symptoms of which patients most frequently complain. Coronary or anginal pain varies greatly in character and severity. At one end of the coronary spectrum is

*Presented as a Morning Lecture at the Thirty-seventh Annual Session of The American College of Physicians, Los Angeles, California, April 17, 1956.

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the classic syndrome of angina pectoris. This is a transitory substernal pressure-pain, which usually is precipitated by some inducing factor, particularly effort or emotion, and is usually promptly relieved by rest or by nitroglycerin. Each attack of angina pectoris represents a momentary state of coronary insufficiency with ischemia. There are no significant abnormal findings on physical examination. The resting electrocardiogram may or may not show changes. Because the resting electrocardiogram is so often normal, the Master Two-step Exercise Test for coronary insufficiency was evolved.⁶

At the other end is the typical attack of acute coronary thrombosis, in which there is a complete closure of an artery. This is usually associated

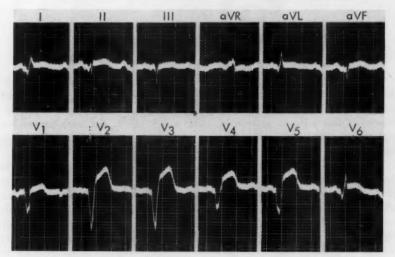


Fig. 1. B. L., m, 54. Acute coronary occlusion. Electrocardiogram (1/3/55, sixth day) indicates massive myocardial infarction (anterior, lateral, diaphragmatic).

with severe or persistent chest pain, changes in blood pressure and heart sounds, heart failure or shock, and a typical electrocardiographic pattern of deep Q waves and RS-T segment elevation, which progresses to T wave inversion (figure 1). This electrocardiogram is practically pathognomonic of acute coronary occlusion with through-and-through infarction; even if the attack is mild, the electrocardiographic pattern is typical. A pericardial rub may be present. Within several days, significant fever, leukocytosis, and changes in the blood "transaminase," fibrinogen, "C-Reactive Protein" and sedimentation rate appear. Many of these alterations persist for days or weeks. The electrocardiographic and fluoroscopic changes are often permanent. Coronary thrombosis occurs spontaneously. There is no precipitating cause except, perhaps, shock." During the attack, peripheral em-

boli may occur. The prognosis is usually good, but death may occur at any time.

Between these two classic types of coronary episodes, the one a very transitory subendocardial ischemia, the other an acute and complete obstruction of a major coronary artery with through-and-through infarction, there is an extremely important, large, variegated group of acute coronary episodes.⁸⁻¹¹ These may be induced or may occur spontaneously. They dif-

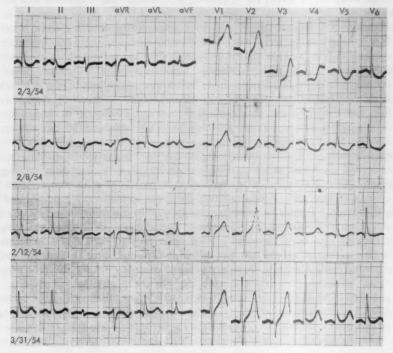


Fig. 2. A. N., m, 39. Acute coronary insufficiency. Angina on effort 8 years. Recent increase in frequency of pain; occurrence at rest and at night, no longer relieved by nitroglycerin. (2/3/54) Two severe, persistent attacks of pain. ECG showed ST depression and T inversion. Marked improvement in nine days, normal in two months.

fer from the classic attack of angina pectoris in that the pain is more prolonged and the electrocardiographic changes may persist for days or weeks. There may be mild fever and a slight leukocytosis. The sedimentation rate may be increased, but is usually no higher than 20 to 30 mm. They differ from attacks of acute coronary thrombosis in that there is usually little alteration in the heart sounds or blood pressure, there is no shock, no heart failure, and no pericardial rub, and peripheral embolism does not occur. Most important, the electrocardiogram shows RS-T depression and/or T

wave inversion, without Q waves; it may return to normal within days or weeks (figure 2). On postmortem examination of these patients, subendocardial necrosis or infarction may be found, but there is no acute thrombosis of a coronary artery.

To this very large group of heterogeneous attacks, which clinically resemble mild coronary thrombosis but can usually be differentiated from it by the electrocardiogram alone, we have applied the term "acute coronary insufficiency." 8-11 From the beginning we realized that this name was not perfect, but it has proved to be a very practical one. Acute coronary insufficiency is a distinct entity, and myocardial injury resulting from it can often be prevented or reversed. Some authors employ the term "coronary insufficiency" to include all coronary episodes, among which is coronary thrombosis. Others prefer to use the term "myocardial infarction" whenever there is evidence of necrosis or infarction, regardless of the presence or absence of coronary thrombosis. 12, 13 However, neither of these two all-inclusive designations seems practical to us. By lumping all cases under one diagnosis, proper therapy for each particular case may not be administered. For those coronary episodes which are characterized by RS-T depression and/or T wave inversions, and in which the prognosis is good, we believe the term "acute coronary insufficiency" is the best thus far suggested. 8-11, 14 Naturally, it is essential that its meaning in this restricted sense be clearly understood, and that the term be employed generally only in this sense. It may be advantageous to modify the term "acute coronary insufficiency" by adding "with ischemia" or "with subendocardial necrosis," as the case may be. Those who insist on employing the expression "myocardial infarction" when this has taken place should qualify the diagnosis as myocardial infarction "secondary to acute coronary insufficiency" or myocardial infarction "secondary to coronary occlusion."

Cases of acute coronary insufficiency fall into two distinct groups on the basis of mechanism or etiology. In the first group a specific precipitating factor, usually extracardiac, determines the severity of the attack; this often can be successfully treated, thereby terminating the coronary insufficiency. This is the group which should be labeled acute coronary insufficiency caused by hemorrhage, shock, paroxysmal tachycardia, emotion, pulmonary embolism, carbon monoxide poisoning, etc., as the case may be. In the second group the acute coronary insufficiency occurs spontaneously, as the result of progressive changes in the coronary arteries. These cases should be termed "spontaneous" coronary insufficiency. It will be useful to discuss these two groups separately.

I. Induced Coronary Insufficiency. This type of acute coronary insufficiency is caused by conditions which increase cardiac work, reduce coronary flow, or alter the oxygen-carrying capacity of the blood. Frequently, a combination of these factors is present. Coronary disease is usually present, but coronary insufficiency may occur in its absence, if the precipitating factor is

sufficiently severe. The conditions which most often induce coronary insufficiency may be listed as follows:

Increased Cardiac Work

Effort
Emotion
Overeating
Hypertensive crisis
Fever and infections
Hyperthyroidism
Paroxysmal tachycardia

Reduced Coronary Flow

Paroxysmal tachycardia Shock Acute hemorrhage Hypotensive crisis Aortic stenosis Pulmonary embolism Insulin shock

Congestive failure Acute abdominal conditions Exposure to heat and cold Excessive smoking Altered Blood

Acute anemia Carbon monoxide poisoning Asphyxia

High altitude Pulmonary insufficiency

In this group of cases, it is advisable to state the precipitating factor in the diagnosis, e.g., acute coronary insufficiency resulting from hemorrhage, 15, 16 shock, or pulmonary embolism, or caused by effort or excitement, or following operation. Such statements will clarify the diagnosis of "acute coronary insufficiency" as we believe it should be clarified, and will direct attention to the need for energetic treatment of the causal condition.

As a rule, acute coronary insufficiency begins to subside when the precipitating condition remits or responds to therapy, e.g., frequent transfusions in acute hemorrhage. If the causative factor is severe enough, death may occur; indeed, coronary insufficiency is the most common cause of "sudden death," as the records of the medical examiner and Armed Forces demonstrate. However, in general, "sudden death" is uncommon. Not infrequently, the precipitating condition masks the presence of the resultant coronary insufficiency, which can then be detected only in the electrocardiogram. It is therefore essential to keep the possibility of acute coronary insufficiency in mind when any one of the conditions which may precipitate it is present.

II. Spontaneous Coronary Insufficiency. Such cases at first usually resemble mild attacks of coronary occlusion. They are best distinguished from the latter electrocardiographically, by the presence merely of RS-T depression and/or T wave change alone. Such attacks have been termed by various authors "coronary failure," 12, 24 "acute atypical coronary artery insufficiency," 25 "minor coronary attacks," 26 and "intermediate coronary syndrome." 27 The prognosis in this group of cases is excellent, and there is, therefore, very little necropsy material. While coronary thrombosis probably occurs in a small number (5 to 10%) of these cases, there is apparently no acute thrombosis in the vast majority of them. The exact anatomic and physiologic mechanisms operating in this group can only be surmised. We, as well as Horn and Finkelstein, have suggested that subintimal hemorrhage may initiate the attack, which does not progress to thrombosis and complete occlusion. 28, 29

This type of case should be distinguished from definite cases of coronary thrombosis, in order to emphasize its benign course, and to realize, therefore,

that treatment may be of short duration, and that some therapeutic measures, such as the administration of anticoagulants, which may be employed in coronary occlusion, are unnecessary. Anticoagulants are unnecessary in acute coronary insufficiency because bed-rest is brief and mural thrombi do not form. The majority of these patients may be permitted to sit in an armchair from the onset of the attack. Actually, it is very likely that many patients with acute coronary insufficiency do not seek medical attention, because of the mildness of their discomfort. It should be emphasized that acute coronary insufficiency may represent the premonitory or initial phase of coronary occlusion ^{28, 29} (figure 3).

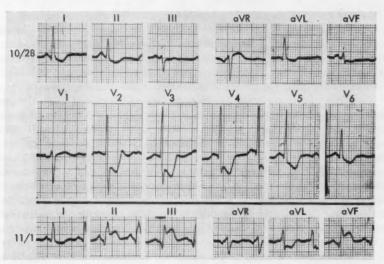


Fig. 3. L. E., m, 52. Electrocardiographic changes of coronary insufficiency during premonitory phase of acute coronary occlusion. (10/28) Onset of substernal pain at rest. Electrocardiogram shows marked ST depressions and T-wave inversions. (11/1) Severest attack of pain. Electrocardiogram shows Q waves and ST elevations in Leads 2, 3 and aVF, indicating diaphragmatic infarction.

INCIDENCE

It is our belief that the incidence of "acute coronary insufficiency" is much greater than is that of coronary thrombosis. Since an attack of "acute coronary insufficiency" is rarely fatal, postmortem studies and statistics to determine its frequency are not reliable. Nevertheless, the pathologic studies which are available, particularly among Armed Forces personnel and in cases of "sudden death" in civilians, indicate that myocardial infarction occurs not infrequently without any thrombosis, i.e., as the result of "acute coronary insufficiency." 30-34

We have estimated that 1,000,000 attacks of coronary thrombosis occur

annually in the United States. It is probable, therefore, that at least 1,500,000 to 2,000,000 attacks of "acute coronary insufficiency" occur each year. This figure is probably not too high, since coronary insufficiency is usually not fatal, since it may be too mild to be detected clinically, and since it is likely that many cases of insufficiency are diagnosed as coronary thrombosis, on the basis of T wave changes alone in the electrocardiogram. Most of these incorrectly diagnosed cases are undoubtedly instances of coronary insufficiency.

HISTORICAL

The concept of "acute coronary insufficiency," as distinct from acute coronary occlusion, first appeared in the German literature in the 1930's. The pioneers were Dietrich and Schwiegk, ³⁵ Büchner ^{36, 37} and Uhlenbruch. ³⁸ Kroetz ¹⁸ believed that "acute coronary insufficiency" occurred as frequently as coronary occlusion, since he found an acute occlusion in 55% of his postmortem cases and an acute coronary insufficiency in 45%. Hallerman ¹⁹ found that 79% of sudden deaths in a series of coroner's cases were caused by coronary sclerosis without thrombosis.

In 1937 we described a fatal case of severe myocardial infarction and acrocyanosis, sh and we reported a case of aortic stenosis which simulated acute coronary occlusion. In neither of these cases was coronary thrombosis found post mortem, and in both the electrocardiogram showed RS-T depressions. In 1940 we reported the case of a 19 year old girl with ulcerative colitis and a hemoglobin of 19%. The electrocardiogram showed RS-T depressions. Postmortem examination showed widespread necrosis of the subendocardial layer and papillary muscles. The coronary arteries were normal. Our major aim has been to emphasize that acute coronary insufficiency should be considered as an entity, with a specific physiology, pathology and electrocardiogram, and often a definite precipitating cause, which also requires proper treatment.

Levy and Bruenn ¹⁷ found no evidence of coronary occlusion in 337 of 376 sudden, fatal cases of acute coronary disease. French and Dock ⁸² reported that there was no evidence of occlusion in 51 of 80 cases of sudden death from coronary disease in young soldiers. Newman ²⁰ stated that postmortem examination of 39 patients who died of coronary disease revealed 29 to be free of a thrombus in the vessels. Moritz and Zamcheck ²² found that there was no coronary occlusion in three fourths of 300 cases of sudden death caused by coronary sclerosis in young soldiers. Munck,²¹ in a study of sudden cardiac deaths, found coronary sclerosis without thrombosis in 255 of 396 patients. Poe ²⁸ failed to find evidence of coronary occlusion in five of nine fatal cases of coronary disease in young men. Master, Carroll and Andrews ³⁹ found a similar incidence in a naval hospital. In a detailed report of 450 autopsies of men who were 18 to 39 years of age and who died of coronary disease, Yater and his co-workers ³⁴ discovered a thrombotic occlusion in 229, only about 50%.

PATHOLOGY

Coronary insufficiency, as a rule, occurs in the presence of coronary disease. It is occasionally encountered in patients with normal hearts, when the precipitating factor is intense, e.g., tachycardia, hemorrhage ⁸ or shock. In mild cases, subendocardial ischemia doubtless occurs, causing the transitory electrocardiographic changes, but no acute alterations occur in the myocardium. When the ischemia is more prolonged, scattered isolated areas of necrosis are present, varying in size from microscopic foci to larger, grossly visible, confluent or disseminated areas (figure 4). The most common sites are the interventricular septum, the papillary muscles of the left ventricle, and the subendocardial layer of the left ventricle, probably because these

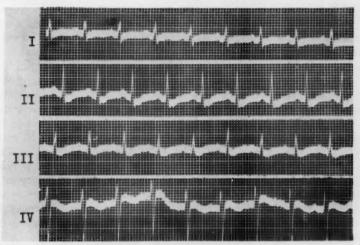


Fig. 4A. T. L., f, 19. Acute coronary insufficiency with subendocardial necrosis in ulcerative colitis and severe anemia. Hemoglobin 14%. Electrocardiogram shows RS-T depression and low T-waves. PM showed microscopic areas of necrosis in anterior and posterior walls and papillary muscles of left ventricle. Coronary arteries normal.

areas are farthest from the larger coronary branches, and because they are exposed to the greatest intramural pressure.¹⁴ The necrotic areas go on to healing and fibrosis.

In the most severe cases the entire inner shell of the left ventricle may be the seat of microscopic confluent necrosis, i.e., "subendocardial infarction." ¹⁴ Very rarely, a through-and-through infarct gradually develops, and the electrocardiogram may then present O waves and RS-T elevation.⁹

Because of the usually good prognosis in the attack of coronary insufficiency, and because of the inadequate search for subendocardial lesions, scanty pathologic material is available, except in cases of sudden death. In this country, two small series of cases of myocardial infarction without acute



Fig. 4B. Microscopic examination showed areas of normal muscle (right upper and left lower corners), and minute, scattered areas of necrosis with hemorrhage and acute and subacute inflammation in the subendocardial layer. The endocardium was intact (extreme upper right-hand corner).

occlusion were published in 1939. 30, 31 These were followed by occasional case reports. 33, 40-42 In one, extensive, confluent subendocardial infarction, extending through two fifths of the thickness of the left ventricular wall, was found, without old or recent coronary occlusion. 41 An infection precipitated congestive failure in this case, and coronary insufficiency resulted. Master and Auerbach's case 38 presented extensive subendocardial necrosis.

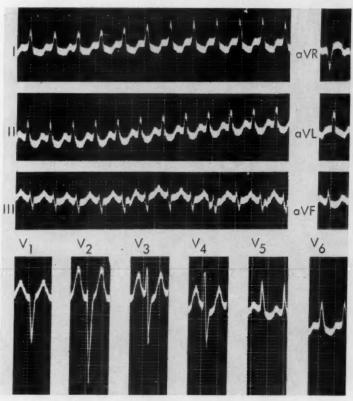


Fig. 5A.

The largest postmortem series was published by our group. It consisted of 25 cases of subendocardial necrosis. In none of these was acute thrombosis found, after very careful study of the coronary arteries. The anterior and posterior papillary muscles were involved 20 times, the posterior portion of the left ventricle 17 times, anterior portion 16 times, the septum 15 times, and the right ventricle only four times. In the majority of these cases the coronary insufficiency was of the secondary type. It was

associated with acute heart failure (5), paroxysmal tachycardia (5), gastro-intestinal hemorrhage (4), pulmonary embolism (3), dissecting aneurysm (2), postoperative shock (1), and severe infection (1). The episode was spontaneous in four instances. The predisposing cardiac lesion was coronary sclerosis, severe in 14 cases, moderate in five, and mild or absent in six. Hypertrophy of the heart was present 22 times. Valvular lesions



Fig. 5B.

Fig. 5. A. D., f, 62. Postoperative supraventricular tachycardia with coronary insufficiency in normal person. A: Electrocardiogram (12/3/50) showed RS-T depression and T-wave inversion in a tachycardia of 210 beats per minute. B: Electrocardiogram (12/4/50) normal following quinidine therapy.

were found in seven of the 25 cases—aortic stenosis (rheumatic) in five, mitral stenosis (rheumatic) in one, and aortic insufficiency (luetic) in one.

Littmann and Barr ²⁵ referred to three cases with extensive subendocardial necrosis, in which only previous coronary occlusion was found. Yu and Stewart ⁴⁰ found no acute occlusion in three of their seven cases of subendocardial infarction. In all these cases the electrocardiogram showed only ST depression and T wave changes, reflecting the localization of the infarction.

Thus, there is usually a close correlation between subendocardial necrosis and RS-T depression in the electrocardiogram, in the absence of acute coronary thrombosis. However, exceptions to this rule occur. Just as acute coronary insufficiency may rarely cause a major infarction, with Q waves and RS-T elevation, so acute thrombosis may exceptionally result in only intramural or subendocardial infarction, with ST depression or T wave changes in the electrocardiogram. Myers, Klein and Stofer reported cases of anteroseptal infarction in which the area involved was a relatively narrow strip near and in the septum. Microscopically, a small area of intramural and patchy subendocardial necrosis was present.

PHYSIOLOGY AND PATHOGENESIS

While acute coronary insufficiency may occur when the heart is normal, 8, 14 it usually is encountered in patients with preëxisting cardiac disease, e.g., coronary disease, luetic ostial stenosis, aortic valvular disease, severe hypertension and cardiac hypertrophy. Chronic anemia and congestive failure also impair the ability of the heart to make adequate adjustments of disturbances in coronary flow. In the presence of any of these conditions, cardiac nutrition is compromised and cardiac reserve is diminished, so that the myocardium readily becomes ischemic. Hence, coronary insufficiency and subendocardial necrosis may be induced or may occur spontaneously.

Acute coronary insufficiency may be induced by conditions which increase cardiac work, decrease coronary flow or alter the composition of the blood. Electrocardiograms in tachycardia and pulmonary embolism are shown in figures 5 and 6. Acute hemorrhage is one of the most important clinical causes of coronary insufficiency, and explains many of the mechanisms involved in producing the ischemia and necrosis. 16, 44-46 Moderate bleeding reduces blood volume, cardiac output and blood pressure; the diminished aortic perfusion results in reduced coronary flow. To compensate for this, the cardiac rate is increased and peripheral vasoconstriction occurs. This may restore adequate circulation. If bleeding continues, however, or if treatment is not instituted, shock ensues. This produces a further diminution in the coronary flow, with a resultant ischemia of the myocardium. As might be expected, the ischemia is most marked in the presence of aortic stenosis, which is associated with marked hypertrophy of the heart and reduced cardiac output. In acute hemorrhage, evidence of coronary insufficiency may appear in the electrocardiogram even before clinical signs appear. It is important to recognize the condition early, since prompt adequate treatment will usually be life-saving. Treatment may be ineffective if delayed until after myocardial involvement has developed.16 The occurrence of anginal pain during hemorrhage makes the need for blood replacement urgent, 15, 18, 47, 48 and this therapy usually promptly relieves the pain.

In coronary insufficiency, localization of ischemia and necrosis in the subendocardial area and in the papillary muscles may be attributed to several factors: the work of the papillary muscles is increased during systolic contraction, the subendocardial layer is remote from the source of blood

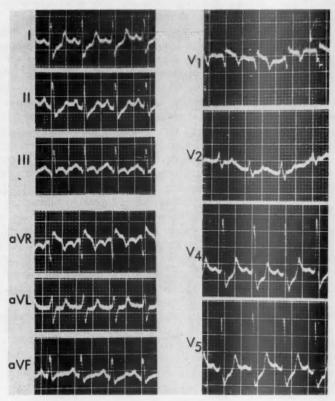


Fig. 6. E. V., f, 40. Acute coronary insufficiency in bilateral postoperative pulmonary embolism in normal person. Electrocardiogram shows large S wave in Leads 1, V_4 and V_8 , and ST depression in Leads 1, V_4 and V_8 . PM showed normal coronary arteries and early subendocardial focal ischemic changes.

supply ³⁰ and has a poor collateral blood supply, ⁴⁹ and the gradient of myocardial pressure during systolic contraction increases from the more superficial layers to the deeper ones. ⁵⁰ Because of the increased pressure exerted upon the subendocardial area during cardiac systole, the pressure in this area is higher than in the left ventricle or in the aorta.

ELECTROCARDIOGRAM

In "acute coronary insufficiency," the electrocardiogram may remain normal or unchanged; presumably, this indicates only a mild degree of subendocardial ischemia or necrosis. This is the type of coronary insufficiency which was termed "coronary failure" by Blumgart and his associates. 12, 24 More commonly, the electrocardiogram shows RS-T depression or T wave inversion, or both. 8-11 These changes may last only several hours or days (when ischemia alone is present), or may persist for several weeks or longer (when definite subendocardial necrosis occurs). In some cases, deeply inverted T waves persist for several months; in some of these cases, the lesion may be a coronary occlusion with localized subendocardial or intramural infarction. In rare cases of coronary insufficiency, Q waves gradually appear, indicating progressive extension of the infarct beyond the subendocardial area, through the myocardial layers. In very rare instances a Q wave and RS-T elevation appear abruptly, simulating acute coronary occlusion with infarction. On very rare occasions also, acute coronary insufficiency induces temporary ST elevation of considerable degree, e.g., during attacks of paroxysmal tachycardia in patients with previous coronary occlusion, following exercise, particularly during the premonitory stage of coronary occlusion, and after smoking.51

As a rule, the electrocardiographic changes appear soon after the occurrence of the "acute coronary insufficiency." Occasionally, they are delayed for several days and, rarely, for one or two weeks.

The RS-T depression and T wave inversion seen in acute coronary insufficiency are usually of mild or moderate degree but occasionally are quite marked. The electrocardiographic changes in acute coronary insufficiency are not specific and do not form a pathognomonic pattern. They are similar to those produced by digitalis, by numerous extracardiac conditions, e.g., infections, acute abdominal diseases and electrolyte disturbances. However, when viewed in conjunction with a clinical picture suggestive of an acute coronary episode, the electrocardiogram in coronary insufficiency is typical, and differentiates it from coronary occlusion in 95% of the cases. 8-11

The association of ST depression with subendocardial involvement is well documented pathologically and experimentally. 52-55 Some doubt has been cast on this relationship recently by the studies of Prinzmetal and his associates, 56 but this work has not yet been confirmed. It is experimental and theoretic, and is not in accord with past clinical and pathologic experience. In digitalis poisoning, it is noteworthy that lesions in the subendocardial area 40 have been found.

TREATMENT

Since coronary insufficiency may be precipitated by various secondary (often extracardiac) conditions, or may occur spontaneously, its treatment varies with the etiologic factor.

A. Secondary Cases. In this group, specific therapy is directed against the particular cause of the acute coronary insufficiency. If the precipitating factor can be eradicated, the acute coronary insufficiency subsides either promptly or gradually. In paroxysmal tachycardia, for example, the blood pressure and the electrocardiogram may return to normal several minutes following the cessation of the rapid heart beat. In this condition, therefore, carotid sinus pressure, digitalis, quinidine, procaine amide, vasopressor drugs, etc., if given in time, arrest the attack and the resultant acute coronary insufficiency (figure 5). In acute gastrointestinal bleeding, repeated transfusions may be required. They should be given until the hemoglobin rises to satisfactory levels; the presence of anginal pain indicates an urgent need for blood. In the presence of severe coronary disease, the amount of fluid injected should be kept as low as possible, and a slow rate of flow should be maintained. Packed red cells are useful to avoid overloading the heart. However, it is remarkable that many units of blood may be administered intravenously without danger, provided they merely compensate for blood lost. Should pulmonary edema occur, it usually responds to morphine, a mercurial diuretic, and other routine treatment for this condition. When shock has precipitated acute coronary insufficiency, the vasopressor amines should be administered immediately. In fact, they should be given even when shock is impending or is suspected, e.g., if the blood pressure is 70 or 80 or even 90 mm. Hg. Infections should be energetically treated with antibiotics; hyperthyroidism with radioactive iodine or other antithyroid drugs; heart failure with digitalis, mercurial diuretics, low salt regime, etc.; hypertensive crises with antihypertensive drugs or removal of a pheochromocytoma, if it is present. Each of the myriad conditions which may precipitate acute coronary insufficiency usually has a specific treatment, or is preventable. Acute coronary insufficiency secondary to pulmonary embolism or infarction, for example, is easier to prevent—by early ambulation and by anticoagulant drug therapy—than to cure.

B. Spontaneous Cases. In this group the cause is coronary sclerosis. Many of these attacks of acute coronary insufficiency are very mild. The patient may not even consult a physician. If he does, he may require only chair rest, but he should be observed for from seven to 10 days; for, although most attacks of coronary insufficiency subside within this time, some may herald the onset of coronary occlusion and major infarction, which may not develop for days or even for several weeks. In mild attacks of acute coronary insufficiency, anticoagulant therapy is not necessary, since the patient rests in a chair for a relatively short period.

Acute coronary insufficiency, however, may be associated with severe, recurrent anginal pain at rest, i.e., status anginosus. This may persist for several weeks or months. In such cases chair rest is usually sufficient; nitroglycerin should be used liberally, and is usually effective; small doses of a narcotic such as codeine, morphine, Pantopon or Dilaudid three or four times daily are frequently helpful. Reassurance is of vital importance.

Most of these cases gradually improve. The pain may disappear completely. Occasionally, however, a coronary occlusion develops. There is considerable difference of opinion concerning the use of anticoagulant therapy in this so-called "premonitory stage of coronary occlusion." In our experience, anticoagulants are not indicated, since most cases subside spontaneously and since anticoagulant therapy has not been successful in preventing the occlusion.

It is thus essential to separate the spontaneous cases of coronary insufficiency from the secondary cases, as well as from cases of coronary occlusion, since the treatment of each group differs. In coronary insufficiency the outlook is excellent, chair rest is usually required for a relatively short period, and anticoagulant therapy is not necessary.

CONCLUSION

Acute coronary insufficiency represents a sudden transitory inadequacy of the coronary circulation for the requirements of the myocardium. It may occur spontaneously or be induced by factors which increase the work of the heart, decrease the coronary flow, or alter the composition of the blood. Usually a combination of these factors exists.

Acute coronary insufficiency is a specific clinical, electrocardiographic and pathologic entity, differing from both angina pectoris and acute coronary occlusion. It indicates a more prolonged and severe myocardial ischemia than does "angina," yet does not present the characteristic electrocardiographic and laboratory features of major infarction secondary to coronary occlusion. There is no change in the heart sounds; there is no pericardial rub, heart failure or peripheral embolization. In coronary insufficiency, mild fever, slight leukocytosis and a slight increase in sedimentation rate may appear, if significant subendocardial necrosis results. At postmortem, no acute thrombus is present in the coronary arteries.

Acute coronary insufficiency is more common than acute coronary occlusion, but may be so mild as to escape recognition. It can develop spontaneously. Often, however, it follows severe hemorrhage, tachycardia, marked physical exertion, emotional upset, trauma (surgical or accidental), sudden hypertension, shock, pulmonary embolism and infarction, severe infections and heart failure. Such cases should be termed "acute coronary insufficiency" secondary to whatever the causative condition may be. Prompt and effective treatment of the precipitating factor may terminate the resultant coronary insufficiency and may even prevent it. In acute hemorrhage, replacement of blood may be life-saving, as are vasopressor drugs in shock and hypotension. The termination of severe tachycardia is also vital. The presence of a precipitating factor in a coronary episode suggests the presence of coronary insufficiency, rather than occlusion. When coronary insufficiency occurs spontaneously, it may clinically resemble coronary occlusion with mild manifestations. However, the electrocardiographic picture usu-

ally serves to distinguish them. Coronary insufficiency may very occasionally cause sudden death; but when the patient survives the onset, the prognosis is better than that following occlusion.

The treatment of coronary insufficiency and coronary occlusion differs, hence the recognition of the former as an entity is essential. In uncomplicated coronary insufficiency, we have employed chair rest or merely house confinement for a period of usually only one to two weeks, avoiding protracted immobilization with the accompanying hazards of peripheral thrombosis commonly seen in older persons. Most patients make a complete recovery and resume work within several weeks. Mural thrombi do not occur in coronary insufficiency, hence anticoagulants need not be administered.

While more than two thirds of the attacks of coronary insufficiency follow a benign course, others are more prolonged and severe and may persist for several weeks or months. An attack of coronary insufficiency may represent the "premonitory phase" of coronary occlusion. Anticoagulant drugs have been recommended in this premonitory or impending phase of acute coronary occlusion but, in our experience, have not prevented the final occlusion.

The term "myocardial infarction" used alone is ambiguous and confuses nomenclature and treatment. If employed, it should be modified, so that the terminology is "myocardial infarction secondary to acute coronary insufficiency" or "myocardial infarction secondary to acute coronary occlusion."

Acute coronary insufficiency, as we have defined it, is a distinct entity with predisposing and precipitating factors, a definite physiopathologic mechanism, characteristic location of the ischemia or necrosis in the subendocardium, and a more or less characteristic electrocardiogram.

Because acute coronary insufficiency can be prevented in the vast majority of instances, and can usually be cured, its clinical recognition and its differential diagnosis from coronary occlusion are essential for definitive treatment.

SUMMARIO IN INTERLINGUA

Acute insufficientia coronari representa un subite inadequatia transitori del circulation coronari quanto al requirimentos del myocardio. Illo forma un entitate clinic, electrocardiographic, e pathologic que differe ab angina de pectore e ab acute occlusion coronari. Illo signala un plus prolongate e sever ischemia myocardial que "angina," sed illo non revela le characteristic aspectos electrocardiographic e laboratorial de major infarcimentos secundari a occlusion coronari. Il non ha friction pericardial, disfallimento de corde, o embolisation peripheric. In insufficientia coronari, leve grados de febre, leve leucocytosis, e un leve acceleration del sedimentation pote manifestar se si significative grados de necrosis subendocardial ha resultate. Al necropsia, nulle thrombo acute se trova in le arterias coronari. Acute insufficientia coronari es plus commun que acute occlusion coronari, sed illo pote esser si leve que illo escappa al observation. Acute insufficientia coronari pote occurrer spontanemente o esser inducite per factores que augmenta le labor del corde, reduce le fluxo coronari o altera le composition del sanguine. Generalmente il ha un combination de iste factores.

Le plus commun conditiones causatori de insufficientia coronari es sever hemorrhagia, tachycardia, marcate effortio physic, disturbation emotional, trauma (chirurgic o accidental), hypertension subitanee, choc, embolismo pulmonar con infarcimento, sever infectiones, e disfallimento cardiac. Casos de iste typo deberea esser designate como "acute insufficientia coronari" secundari a sia que sia le condition causative. Un prompte e efficace tractamento del factor precipitatori pote terminar (o prevenir) le resultante insufficientia coronari.

Ben que le majoritate del attaccos de insufficientia coronari seque un curso benigne, alteres es plus prolongate e sever e pote persister durante plure septimanas e menses. Un attacco de insufficientia coronari pote representar le "phase premonitori" de occlusion coronari.

Le termino "infarcimento myocardial" usate sol es ambigue e confunde le nomenclatura e le therapia. Si le termino es usate del toto, on deberea modificar lo como "infarcimento myocardial secundari a acute insufficientia coronari" o "infarcimento myocardial secundari a acute occlusion coronari."

Acute insufficientia coronari, secundo le definition usate per nos, es un distincte entitate con factores de predisposition e de precipitation, con un definite mechanismo physio-pathologic, un characteristic location del ischemia o necrosis in le subendocardio, e un plus o minus characteristic electrocardiogramma.

Proque acute insufficientia coronari ha usualmente un prognose benigne e pote esser prevenite o mesmo curate, su recognition clinic e su diagnose differential ab occlusion coronari es de alte importantia.

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SOME OUANTITATIVE ASPECTS OF TREATMENT WITH QUINIDINE * †

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Even a cursory review of the literature will make it clear that there is great variability in the use and dosage of quinidine in this country. Opinion differs greatly as to the value of the drug, and the concepts of the risks involved vary from one medical center to another. This state of affairs is true even though the drug has been used rather abundantly in the past 35 years. In the present communication we hope to reconcile some of these differences and to summarize some of our work, where the emphasis in the use of quinidine has been placed on concentration in the blood rather than on dose. Reliance on dosage alone has been customary by many clinicians; we believe that the conversion of chronic auricular arrhythmias, the prevention of recurrent arrhythmias and the occurrence of toxicity are related more closely to the concentration of quinidine in the blood than to the dose. earlier reports stressing the toxic effects of the drug did not emphasize the need for general measures, including full control of cardiac failure, if present, prior to the use of quinidine. Fahr's experience in this regard is quite illuminating. In an early study he described a high incidence of cardiac failure and toxicity resulting from the use of quinidine; in a later report he stressed the point that, when general measures and treatment of cardiac failure were instituted first, the incidence of toxicity was exceedingly low.1

QUINIDINE BLOOD LEVELS

Ouinidine can be determined in the blood quite readily by fluorometric technics. Ouinidine fluoresces in acid media, and the degree of this fluorescence can be measured in a Coleman fluorometer, as was first shown by Brodie.2 Utilizing such measurements, we have found that the concentration of quinidine in the blood achieved with equal doses of the drug varied strikingly in different individuals. This was true with both large and small doses, although in general the larger the dose, the higher the concentration attained. For example, we have observed a fivefold difference in serum concentrations resulting from doses of 3 gm. per day. Striking differences may also be achieved when maintenance doses such as 0.4 gm. four times

^{*} Presented at the Thirty-seventh Annual Session of The American College of Physi-

cians, Los Angeles, California, April 17, 1956. From the Department of Medicine, University of California School of Medicine, San Francisco, California.

[†] Aided in part by grants from the Placer County, California, and the San Francisco Heart Associations.

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a day are used. This variability in serum concentration on identical dose schedules may explain some of the vagaries of clinical response when the

drug has been used empirically.

Our experience indicates that the serum concentration is related both to conversion of an arrhythmia and to toxicity.³ When progressive doses of quinidine are given, conversion or toxicity (if it occurs) is usually to be expected within four hours of the maximal serum concentration. This is not invariable, however, since in about 15% of conversion attempts, return to sinus rhythm will occur with falling blood levels during the night.

Serum studies have shown that the peak concentration reached after an individual dose occurs in about two hours; this is the interval we have found most effective for spacing doses. If the drug is given more often than five or six times at two-hour intervals, metabolic breakdown and excretion balance absorption of quinidine and no further rise in concentration occur. To effect a further rise in serum concentration the size of the individual dose must then be increased or the intervals between doses shortened. If the drug is being given every four hours, or four times a day, the balance between metabolic breakdown and absorption takes place more slowly, and equilibrium is reached in 48 to 72 hours.

TOXICITY

Since the toxic effect of quinidine is the factor of chief concern to most physicians, this will be discussed first. Toxicity is manifested in a variety of ways. The rarest results from true sensitivity or idiosyncrasy to the drug, and is usually manifested by fever, purpura, rashes or marked hypotension, which can be induced by a small initial dose. For this reason a test dose of 0.2 gm. of quinidine is advisable before starting treatment. Toxicity can be further subdivided into the mild variety, which occurs in many patients and rarely is an indication for stopping the drug. It is manifested by mild nausea or diarrhea, and occasionally by headache or tinnitus. A further degree of toxicity, which we classify as moderate, and which again rarely requires cessation of quinidine unless seriously disturbing to the patient, is evidenced by more nausea and perhaps vomiting, more prominent diarrhea, more disturbing lightheadedness and tinnitus, and electrocardiographically by an increase of QRS width of from 25 to 50%. The symptoms and electrocardiographic findings are an indication of quinidine effect and, unless the vomiting or diarrhea is severe, are not indications to stop the drug. It is advisable to attempt to treat these gastrointestinal symptoms by various measures, such as sedation, paregoric or Thorazine, before continuing the attempt at conversion. We classify toxicity as myocardial if the electrocardiogram shows frequent ventricular premature beats (one or more every six beats), an increase of QRS width of 50% or more, complete AV block, ventricular tachycardia or ventricular fibrillation. In

many such cases the toxicity will be recognized by electrocardiographic changes only, and the patient will be unaware of it. When these myocardial manifestions of toxicity are present, it is our policy to discontinue the therapeutic attempt with quinidine or to decrease the amount of the drug.

These electrocardiographic manifestations of quinidine toxicity may result from small as well as relatively large doses of quinidine. We have attempted to determine under which circumstances we can expect their occurrence, since this is the form of toxicity that concerns us the most. We therefore tabulated all the determinations of serum quinidine concentration made during attempted conversion of chronic auricular fibrillation in the last six years and related them to the presence or absence of electrocardiographic or clinical toxicity. In approximately 700 serum determinations we found that only three cases of myocardial toxicity had occurred at serum levels less than 6 µg per milliliter, and none at less than 3 µg per milliliter. The incidence of myocardial toxicity increased progressively as the serum concentration exceeded 6 µg per milliliter; it rose to 12% at levels between 6 and 8 µg, 30% between 8 and 10, 45% between 12 and 13, and 65% at levels over 14. Since the serum concentration in different patients may vary disproportionately to the size of the dose of the drug, the serum levels give a more reliable indication of when toxicity is likely than does the dose of the drug itself. In patients with chronic auricular fibrillation who had been given quinidine to achieve sinus rhythm, myocardial toxicity occurred only in those whose serum concentration was higher than 6 µg per milliliter, with the exception of three instances, despite the fact that the dose varied considerably.

The serum concentration, while more important than dose per se, should not be considered the only factor influencing toxicity. The underlying degree of cardiac disease, the presence of cardiac failure, the depletion of electrolytes or vitamins, the presence of acute infections, all influence toxicity. Accordingly, patients may respond differently on different occasions and at varying serum levels.

CHRONIC AURICULAR FIBRILLATION

We may now proceed to a discussion of the use of quinidine in the conversion of chronic auricular fibrillation to sinus rhythm. This has been a thorny and controversial subject for many years. We have recently completed a study of 214 conversion attempts in 177 patients.³ Conversion was attempted by one of two technics: (1) the rapid method—0.4 gm. every two hours for five doses, repeated the next day, then increased to 0.6 gm. every two hours for five doses if warranted by the patient's response and the absence of toxicity; (2) the slow method—0.4 gm. four times a day for 72 hours, increased to 0.6 gm. four times a day for 72 hours, and then to 0.8 gm., etc., depending upon the response and lack of toxicity. The

patients were observed closely before each dose, and electrocardiograms were taken daily during the conversion attempt. It was found that 80% of all conversions without clinical toxicity occurred with doses of 3.0 gm. of quinidine per day or less, or at serum concentrations of 8 μ g per milliliter or less. Since the toxicity from quinidine increases progressively as this dose or this level is exceeded, the relatively small yield of 20% additional conversions with larger doses should be kept in mind, and the relative chances of conversion weighed carefully against the relative risks of toxicity.

Various factors influencing conversion were studied, and it was found that the four factors which proved to be adversely significant were: rheumatic etiology; duration of fibrillation longer than six months, and especially longer than a year; the presence of cardiac failure which did not respond to the usual measures of therapy; and mitral insufficiency (table 1). The over-all conversion rate in the total series was approximately 75%,

TABLE 1
Factors Adversely Affecting Conversion of Auricular Fibrillation with Quinidine

	Significance (p value
1. Rheumatic etiology	< 0.001
2. Duration of auricular fibrillation more than 6 months	< 0.001
3. Presence of significant or predominant mitral incompetence when compared to nonrheumatic heart disease	< 0.001
Presence of significant or predominant mitral incompetence when compared to pure mitral stenosis	0.015
Presence of cardiac failure at the time of the attempt	0.02

but the incidence varied from 95% in patients without cardiac failure and with fibrillation of short duration to approximately 45% in patients with mitral regurgitation, with or without cardiac failure. These figures are important in aiding the physician to evaluate the relative hazards of the drug compared to the potential benefits of conversion.

RELAPSES

Many physicians believe that the value of attempts to convert auricular fibrillation to sinus rhythm is negated by the fact that the patients will relapse back to fibrillation very promptly. We attempted to evaluate this factor in approximately 100 cases. Although it was difficult to control the patients completely, we found that of the 100 patients in whom sinus rhythm had been restored, 85% relapsed promptly if no maintenance dose of quinidine was given, or if the maintenance dose was discontinued. When varying maintenance dose schedules were used, the incidence of relapse also varied,

depending upon the preventive dose of quinidine used and the percentage sustained by the maintenance dose schedule. In general, a daily dose of 0.4 gm. four times a day, or a serum level which averages 60% of that required for converting the original arrhythmia, will usually prevent relapses as long as the cardiac status remains the same. If the cardiac disease worsens, if the myocarditis or mechanical factors influencing the heart progress, or if the degree of coronary sclerosis advances, patients may break through the quinidine barrier. In those cases in which 0.4 gm. of quinidine four times daily failed to maintain sinus rhythm, the serum levels were often low.

RECURRENT ACUTE ARRHYTHMIAS

Recurrent paroxysmal arrhythmias are a common problem facing the physician. A study of the quinidine concentration in the blood in patients receiving the usual therapeutic doses, however, often explains many therapeutic failures. For example, when paroxysmal fibrillation or paroxysmal tachycardia recurs in patients who are being given small doses, such as 0.2 gm. three or four times a day, it will frequently be found that the failure to prevent the attacks is related to low serum concentrations. We have often noted in these patients that the midday serum concentration of quinidine is relatively low on the ordinary dose of 0.2 to 0.4 gm. three times a day. Maintenance doses of 0.4, 0.6 or even 0.8 gm. four times a day may be required to prevent recurrent attacks of any type of paroxysmal arrhythmia. In one patient with ventricular tachycardia, a daily dose of 3.2 gm. was required to achieve serum concentrations above 4 µg per milliliter, a level which we have found is generally required to prevent these arrhythmias. In another patient with paroxysmal auricular fibrillation, various physicians over a period of 12 years had used ordinary therapeutic doses of quinidine (0.2 or 0.3 gm. three times daily) without successfully preventing attacks. It was then discovered that the patient's serum concentration of quinidine was only 2.0 or 3.0 μ g per milliliter on these doses. When the patient was given 0.6 gm. four times a day the serum concentration rose to approximately 5.0 µg per milliliter, and the attacks were completely prevented. The same experience was true of patients with premature beats or paroxysmal flutter. Since a plateau in serum concentration is reached after about 72 hours when any dose of the drug is given at fixed intervals, it is important to determine the serum concentration 72 hours or more after the fixed dose schedule. If this dose and serum level have proved inadequate, one must increase the size of the dose or decrease the interval between doses to achieve the levels which prevent paroxysmal arrhythmias.

PARENTERAL QUINIDINE

Patients, on occasion, are unable to tolerate oral quinidine because of vomiting or diarrhea, or because they are seriously ill with an acute ar-

rhythmia. Parenteral quinidine, usually intramuscularly, can be given in these circumstances. A variety of preparations is available, and we have found the most satisfactory one to be quinidine gluconate (Lilly).4 With this preparation, 0.8 gm. of quinidine gluconate is equivalent to 0.6 gm. of quinidine sulfate in terms of quinidine base. The peak concentration in the serum occurs about two hours after an oral dose; in contrast, the maximal concentration occurs in about one hour with quinidine gluconate given intramuscularly, and the rise in serum concentration is considerably higher. Therefore, one may use quinidine gluconate intramuscularly at intervals of one or two hours to treat an acute arrhythmia. We rarely give more than three, or at the most four, injections at one or two hour intervals because the serum concentration rises quite rapidly and hypotension may result, although rarely of the degree caused by intravenous injections of procaine amide. If the clinical condition warrants, the drug can then be given orally, or the interval between the doses decreased. In a series of patients with acute paroxysmal arrhythmias, conversion to sinus rhythm often occurred within one or two hours after the initial dose of the drug. Intravenous quinidine is used only in urgent situations; we have found that it may be effective when the drug cannot be tolerated orally. The usual dose is 0.8 gm. of quinidine gluconate diluted to 50 ml. with glucose solution, given very slowly at a rate not exceeding 1 or, at the most, 2 ml. per minute. An electrocardiogram should be taken continuously during the infusion, and an assistant should monitor the blood pressure and electrocardiographic response. Hypotension occurs much more often with frequently repeated parenteral doses of quinidine, whereas it is less common with oral quinidine.

CONCLUSION

Serum quinidine concentrations are often helpful in aiding the physician in the most effective use of quinidine. Knowledge of the serum level allows more rational treatment of both acute and chronic arrhythmias, and permits a clearer awareness of the possibility of toxicity. The physician who appreciates the quantitative aspects of the use of quinidine will be in a better position to weigh the relative risks of the drug against the potential benefits to be gained. Control of therapy through knowledge of the serum quinidine concentration should decrease the risk of toxicity to the patient and permit safer and more effective therapy.

SUMMARIO IN INTERLINGUA

Le therapeutica rational ha semper profitate del determination del concentration del agente in le sanguine. Quinidina se mesura satis facilemente per su fluorescentia in medios acide.

Es presentate observationes que permitte le establimento de relationes inter le dose de quinidina, le concentration de quinidina in le sanguine, e le effectos therapeutic e toxic de quinidina.

Le concentration seral medie de quinidina in un gruppo de patientes se augmenta quando le doses del droga es augmentate, sed le valores pro le patientes individual monstra considerabile variationes. Per exemplo, un dose diurne de 3 g de quinidina pote resultar in un patiente in un concentration seral cinque vices plus alte que in un altere patiente. Le toxicitate myocardial es correlationate con le nivello seral de quinidina plus tosto que con le doses individual del droga. Iste toxicitate es incommun con concentrationes seral de minus que 6 mcg per ml e deveni progressivemente plus marcate in tanto que le concentration monta supra ille valor. Le incidentia de toxicitate satis sever pro requirer le cessation del administration del droga monta ab 1% pro nivellos infra 6 mcg per ml a 8, 16, 25, e 38%, respectivemente, pro nivellos de 7, 8, 9, e 10 mcg per ml.

Le factores que influentia le successo del conversion de chronic fibrillation auricular es discutite in le lumine de nostre experientias con 215 essayos de effectuar conversion per medio de quinidina. Le sequente factores reduceva le probabilitate de successo in le effortio de effectuar conversion: insufficientia mitral, fibrillation auricular de plus que un anno de duration, e disfallimento cardiac. Casos de non-rheumatic morbo cardiac o de noncomplicate stenosis mitral esseva convertite con

bon successo in al minus 85% del patientes.

Novanta pro cento de omne casos chronic de fibrillation auricular convertite a rhythmo sinusal attinge iste conversion a nivellos seral de quinidina de infra 10 mcg per ml. Le decision de si o non on debe continuar le effortio a effectuar un conversion quando 3 g de quinidina ha essite administrate diurnemente o quando le nivello seral del droga attinge nivellos de 8 o 10 mcg per ml presuppone que on es familiar con le facto que le toxicitate cresce e que le probabilitate de successo in effectuar conversiones decresce quando le mentionate dose e le mentionate concentration seral es superpassate.

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THE CLINICAL SIGNIFICANCE OF THE ELASTIC PROPERTIES OF THE LUNG*

By RICHARD V. EBERT, M.D., F.A.C.P., Little Rock, Arkansas

In recent years there has been an expanding interest in the clinical application of pulmonary physiology. Pulmonary function tests have become widely used, and these studies have been of aid in the diagnosis and management of patients with chronic pulmonary disease. The elasticity of the lungs plays an important rôle in the normal functioning of this organ. If the lungs possessed no elastic properties breathing would be impossible.

Before discussing the elastic properties of the lung it is probably wise to define the term elasticity. If a wire is stretched it will tend to return to its original length after release. The force producing the stretch is termed the stress, and the change in length, the strain. Within limits the strain will be proportional to the stress. It should be emphasized that measurements are made under static conditions. No motion is involved, and the impressed force and the force resisting deformation are in balance.

Perhaps the simplest way to illustrate the principles involved in a study of the elastic properties of the lung is to compare it to a balloon. This has some validity in that Lawton 1 has demonstrated that the elastic properties of the lung are similar to those of a rubber balloon. A balloon can be inflated in two ways. Positive pressure can be applied to the mouth of the balloon, thus causing inflation (figure 1). Alternatively, the balloon can be placed in a box with the mouth of the balloon projecting into the atmosphere and negative pressure applied to the outside of the balloon. The latter method resembles the lungs in the closed chest. In either case the pressure difference between the inside and outside of the balloon constitutes the stress. The change in volume of the balloon constitutes the strain. Measurements must be made under static conditions.

If the volume of the balloon is measured at various levels of pressure and a plot of pressure and volume made, an S-shaped curve will be obtained. The midportion of the curve is relatively linear. The slope of this portion of the curve can be described as change in volume in liters per 1 cm. of water change in pressure. This is termed compliance. In any case, it is important to state the volume at which the slope of the curve is defined, as the curve is not linear.

^{*}Presented at the Thirty-seventh Annual Session of The American College of Physi-

cians, Los Angeles, California, April 19, 1956.

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Studies of the elastic properties of the lung are performed in a similar manner. The intrathoracic pressure and the volume of the lung are measured. The difference between the intrathoracic pressure and mouth pressure is assumed to represent the pressure distending the lung. All pressures are measured under static conditions. This can be done by measuring the pressure at the end of inspiration and expiration, using a pneumotachograph as an indication of the time of zero flow. Alternatively, the movement of air can be stopped by means of a valve.

The chief problem has been the measurement of intrathoracic pressure. The obvious method is to create a small pneumothorax and measure intrapleural pressure. This was done by such earlier workers as Neergaard and Wirz,² Christie,³ Paine ⁴ and, more recently, Dayman.⁵ Unfortunately, the technic involves some hazard to the patient, particularly those with pulmonary emphysema. To overcome this disadvantage a method has been

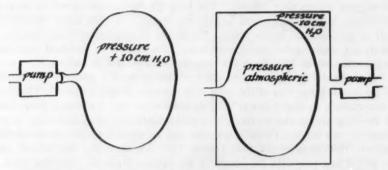


Fig. 1. Inflation of a balloon by positive pressure on the inside and by negative pressure on the outside of the balloon.

devised using intra-esophageal pressure as a measure of intrathoracic pressure. When free of peristaltic activity, the esophagus is a flaccid tube which transmits the intrathoracic pressure to a balloon lying within it. This method was first used for studying lung elasticity by Buytendijk on Holland. It has subsequently been widely applied in England and in this country. T, 8, 0

If the curves obtained from intrapleural measurements are compared with those obtained from intra-esophageal pressure measurements, it will be noted that the shape of the curve is similar, although the absolute pressure differs somewhat.⁷ Cherniack ¹⁰ made a systematic comparison of intrapleural and intrathoracic pressures, and found that intra-esophageal pressure was usually more positive than intrapleural pressure. In spite of this discrepancy, it would appear that intra-esophageal pressure measurements provide us with valuable data regarding the elastic properties of the lung.

If we analyze the pressure volume relationship of the lung in the normal

human being, we note that the midportion of the curve is relatively linear (figure 2). Near the residual volume the intrathoracic pressure approaches atmospheric pressure. As the volume of the lung approaches the total lung capacity, the intrathoracic pressure becomes markedly negative and the slope of the curve changes in this area so that a greater change in pressure is required to produce a given change in volume. In a group of normal subjects studied by Stead, Fry and Ebert, the slope of the curve in its midportion expressed as compliance was 0.23 L. per 1 cm. of water change in pressure. This corresponds closely to the results obtained by Mead, Lindgren and Gaensler.

A few comments regarding the factors responsible for the elasticity of the normal lung may be worth while. Certainly the elastic tissue contained

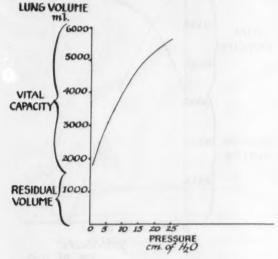


Fig. 2. Pressure volume curve of the lungs of a normal human being.7

in the lung must contribute to an important extent. The elastic tissue is related to the bronchi and is found in the alveolar walls. The blood vessels contribute and, as will be mentioned later, the pressure within the vessels bears a relationship to the elastic properties of the lung. Finally, there is evidence that the surface energy of the air liquid interface in the alveoli contributes significantly to the elasticity of the lung.¹¹

A study of the elastic properties of the lung is of great importance in pulmonary emphysema. Since the time of Laennec it has been known that the lungs in emphysema do not collapse in a normal manner when the chest is opened. Moreover, clinical and physiologic studies indicate that the lungs in emphysema are overdistended and that the residual volume is in-

creased. On this basis, it has been assumed that drastic alterations in pulmonary elasticity were present. The hazard of measuring intrapleural pressure in this disease impeded progress in the study of lung elasticity. The development of the intra-esophageal pressure method permitted extensive studies without endangering the life of the patient.

Figure 3 illustrates the characteristic change in the pressure volume relationship of the lung in emphysema. A uniform finding in emphysema is an increase in residual volume and reduction in vital capacity. The total lung capacity is normal or increased. In association with the increase in

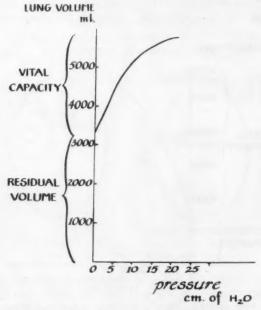


Fig. 3. Pressure volume curve of the lungs of a patient with pulmonary emphysema.

residual volume there is an upward shift of the pressure volume curve. This means that a given pressure will produce a greater distention of the emphysematous lung than of the normal lung. Curiously enough, the shape of the curve is not dissimilar to that of the normal lung. Moreover, the slope of the curve in its midportion or compliance is not greatly different from that of the normal lung. In a group of patients with emphysema the compliance was found to be 0.18 L. per 1 cm. of water change in pressure. These measurements were made under static conditions. Mead, Lindgren and Gaensler 12 noted similar values for compliance under these conditions but found the compliance to be markedly decreased with hyperventilation. This

discrepancy is probably related to the uneven alveolar ventilation in emphy-

The importance of the elasticity of the lung in breathing cannot be overemphasized. If the lungs did not have elastic properties the intrathoracic pressure would not be negative, and movement of air in and out of the lungs would be impossible. The essential rôle of the elasticity of the lung in breathing is illustrated by the deficit in ventilation of the lungs in pulmonary

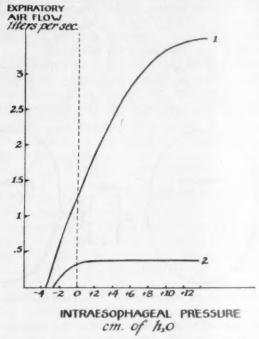


Fig. 4. The relationship between expiratory air flow and intrathoracic pressure. The measurements are all made at a constant level of inflation of the lung. The difference between the pressure at zero flow and the pressure at any given level of flow represents the pressure applied to produce movement of air from the lung. 1. Normal subject. 2. Patient with emphysema.¹⁸

emphysema. The difficulty in breathing in emphysema is related to decrease in the maximal rate of expiratory air flow. This, in turn, is responsible for the reduction in maximal breathing capacity and ratio of one second to total vital capacity.

In discussion of the effect of lung elasticity on expiratory air flow it is necessary to describe the factors influencing the movement of air in and out of the lung. The rate of air flow in the trachea is determined by the gradient of pressure between the mouth and alveoli and the resistance to flow

in the air passages. In the normal lung the resistance to air flow is relatively small, and high rates of air flow can be achieved with relatively small gradients of pressure (figure 4). The resistance to flow is considerably increased in pulmonary emphysema.¹³ Moreover, the pressure flow curves during expiration exhibit an asymptote. A point is reached at which further increase in pressure causes no increase in rate of flow. This is illustrated in figure 4. It will be noted that when the intrathoracic pressure is negative, increase in pressure causes an increase in rate of flow. When the intrathoracic pressure becomes positive, further increase in pressure causes no further increase in flow. This is true even when very large positive pressures are applied to the lung. Dayman,⁵ the first to describe this phenomenon, referred to it as the check valve mechanism.

An understanding of the phenomenon is of the greatest importance. The obstruction to air flow in emphysema appears to be in the bronchioles. These are unsupported by cartilage and hence can be readily collapsed. Apparently they are collapsed when the intrathoracic pressure becomes positive.

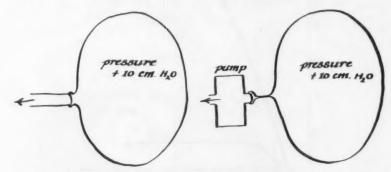


Fig. 5. Effect of negative pressure applied to the mouth of a rubber balloon.

The reason for this can perhaps be best understood by again referring to the analogy of the balloon. An inflated balloon with a neck of rubber will empty if the orifice is opened (figure 5). The rate of emptying will depend on the elastic properties of the balloon and the resistance to air flow offered by the neck. If we attempt to hasten the flow of air from the balloon by attaching a pump to the neck, nothing is accomplished. The negative pressure created by the pump merely collapses the neck of the balloon.

From these considerations we can conclude that in bronchiolar obstruction the limit of expiratory air flow is the rate of flow achieved by the freely collapsing lung. This, in turn, simplifies the problem, because the maximal air flow will be dependent upon the elastic pressure of the lung and on the resistance to air flow in the air passages, together with any frictional resistance of lung tissue. The rate of air flow at various levels of inflation of the chest will be a function of the pressure volume curve of the lung.

Thus the maximal rate of air flow will be much greater with the chest in the position of marked inspiration than in the expiratory position. The clinical implications of these observations are apparent. The effect of bronchiolar obstruction will be much more severe in those patients with impaired pulmonary elasticity than in patients with normal lungs. The interrelationship between bronchial asthma and pulmonary emphysema is clarified. It must be remembered that in obstruction to the major bronchi or trachea, positive intrathoracic pressure does enhance expiratory air flow. This is because these structures are supported by cartilage.

In the previous discussion we have referred to the pressure volume relationship of the lungs as a whole. Each unit of the lung will have its own pressure volume curve. In the normal lung the elastic properties of the various portions of the lung must be remarkably uniform. If this were not true the alveoli would be unequally ventilated. On the other hand, there is much evidence that in pulmonary emphysema the lung is unequally ventilated. Some portions of the lung are hyperventilated and others poorly ventilated. It is this unequal ventilation of the lung, together with unequal perfusion of alveoli with blood, which is believed to be responsible for the hypoxia and hypercapnia in patients with emphysema. The bullae represent areas of lung tissue which have almost totally lost their normal elastic properties.

Another implication of the unequal elastic properties of various portions of the lung in emphysema is the unequal rate of deflation of various portions of the lung during expiration. Each segment of the lung will deflate at a rate determined by the pressure volume relationship for that segment and by the resistance to air flow in the bronchiole supplying that portion of the lung. Mead ¹² has pointed out that this difference in time required for deflation in different parts of the lungs means that the areas ventilated will vary with the rate of breathing. With rapid breathing the areas with impaired elasticity and obstruction will empty poorly during expiration, and hence ventilation will be largely confined to the more normal portions of the lung.

Finally, mention should be made of the change in the elastic properties of the lungs in patients with heart disease. Dyspnea is a characteristic symptom of heart failure. The degree of dyspnea is correlated with the reduction in vital capacity. The total lung capacity is reduced and the residual volume is normal. Examination of the pressure volume curves of the lungs of patients with heart failure reveals a decrease in compliance ^{14, 15} (figure 6). Less change in volume is produced by a given change in pressure than in the normal lung. The change in compliance is closely related to the change in vital capacity. This can be demonstrated by plotting the pressure volume curves for normal lungs and lungs of patients with heart failure against per cent vital capacity. The two curves are almost exactly superimposed.

The alteration in pulmonary elasticity in heart failure is related to

changes in pulmonary vascular pressure and pulmonary blood volume, and to pulmonary edema. There is considerable evidence relating pulmonary blood volume to vital capacity. In general, factors which decrease pulmonary blood volume increase the vital capacity, and those which increase pulmonary blood volume decrease the vital capacity. Recently Hickam ¹⁶ has shown that application of a G suit and consequent shifting of blood to the lungs causes a sudden decrease in pulmonary compliance. Alteration in pulmonary blood volume and pulmonary vascular pressures does not seem to be the entire mechanism producing the reduction in vital capacity and change in pulmonary elasticity. Clinical evidence would indicate that

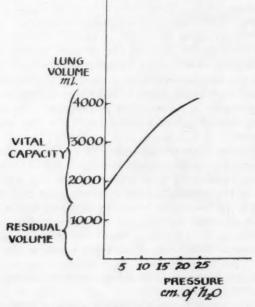


Fig. 6. Pressure volume curve of the lungs of a patient with heart failure.14

pulmonary edema plays an important rôle. It would appear that the reduction in vital capacity persists for a reasonably long period of time after an episode of acute pulmonary edema. The rather poor correlation between the vital capacity and pulmonary arterial pressure in patients with heart failure would support the importance of pulmonary edema.

SUMMARIO IN INTERLINGUA

Le pulmones se comporta como un corpore elastic. Il es possibile preparar pro le pulmone un curva pression-volumine que defini le proprietates elastic del pulmone. Isto es effectuate per mesurar le volumine de inflation del pulmones e le pression intra-esophagee. Le proprietates elastic del pulmones del patiente con

emphysema differe ab le proprietates elastic de pulmones normal. In patientes con emphysema le pression intrathoracic es minus negative pro un date volumine pulmonar que in individuos normal.

Le alterate elasticitate del pulmone in emphysema contribue al obstruction del fluxo de aere expirate. Il pare que le volumine maximal del fluxo expiratori de aere es un function del pression elastic del pulmone e del resistentia contra le fluxo aeree in le vias respiratori. In emphysema, tanto le defective elasticitate como etiam le augmentate resistentia contra le fluxo aeree in le bronchiolos contribue al sever limitation del volumine maximal del fluxo expiratori de aere. Un altere aspecto importante del pulmone in emphysema es le non-uniforme alteration del elasticitate de varie portiones del pulmone. Isto resulta in alterate relationes de ventilation e perfusion.

Le proprietates elastic del pulmone es etiam alterate in patientes con congestive disfallimento cardiac. Le accomodation es reducite, e per consequente un date alteration de pression produce un minus grande alteration del volumine que in pulmones normal.

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NONTUBERCULOUS PULMONARY CAVITATION IN ANTHRACOSILICOSIS*

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It is the primary purpose of this paper to emphasize the occurrence of "nontuberculous" ischemic cavitation in conglomerate masses of third-stage anthracosilicosis. Ten such cases will be presented. In view of the tendency to consider such cavities tuberculous, the adjective "nontuberculous" is used deliberately to point out what these cavities are not, while the adjective "ischemic" is used to shed some light upon what may be their true nature. We were afforded an excellent opportunity of investigating the problem of cavitation in third-stage anthracosilicosis since this hospital, situated as it is in the heart of the coal mining region, admits a large number of patients with anthracosilicosis. Between November, 1950, and March, 1956, approximately 1,200 cases of anthracosilicosis in all stages were seen. Of these, 24 were complicated by tuberculosis, proved by positive bacteriology, an incidence of approximately 2%; and 10 proved to have nontuberculous cavities, an incidence of approximately 1%.

Clinical differentiation between these two groups was made on the basis of repeated examinations for acid-fast bacilli, which comprised sputa smears and cultures and gastric cultures. It was felt that differentiation could be made on this basis, since it has been acknowledged that the finding of tubercle bacilli in tuberculous cavitation of the lungs is extremely high. It might be said with only slight fear of contradiction that the absence of tubercle bacilli in the sputum of a patient presumed to have a tuberculous cavity, whether associated with anthracosilicosis or not, is practically incontrovertible evidence that the cavity is due to another cause. It is not held, of course, that acid-fast bacilli will be found in the sputum of a patient with an unexcavated tuberculous conglomerate nodule, in which the tubercle bacilli are imprisoned.

Though the chest x-ray film cannot definitely differentiate tuberculous from ischemic cavities, it can prove to be of some help. A cavity in a silicotic lung outside a large conglomerate mass or within a relatively small conglomerate nodule, to which the blood supply is probably adequate, is definitely not ischemic in origin. It is probably due to another cause, such as tuberculosis, lung abscess, carcinoma or fungus disease. During the last year we have seen at this hospital two cases of lung abscess, one associated

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with second-stage anthracosilicosis and the other with third-stage anthracosilicosis, with the cavity in the latter case not in proximity to the relatively small conglomerate nodule. On the other hand, a cavity in a large conglomerate mass, seen on x-ray as a translucency at the upper pole of the mass and at times associated with a fluid level, is usually either tuberculous or ischemic.



Fig. 1. Case 1. November 20, 1951. Erect postero-anterior film of chest showing bilateral anthracosilicotic conglomerate nodules.

In four out of the 10 cases that came to autopsy, further proof was afforded in support of the nontuberculous nature of the cavitation by the postmortem findings.

CASE REPORTS

Case 1. The patient, age 56, a white male hard coal miner for 25 years, was hospitalized here on four occasions: in 1951 and 1953, and twice in 1954. His chief

complaint on each occasion was exertional dyspnea, present for many years. In 1951 he was considered to have third-stage anthracosilicosis and pulmonary emphysema, the pulmonary function tests disclosing moderate impairment of ventilation, obstructive in type. During the last three hospitalizations he was also found to have cor pulmonale in failure. In addition, in 1953 he developed a nontuberculous cavity on the right. During his four hospitalizations, repeated sputa smears and cultures and gastric cultures were negative for acid-fast bacilli. In 1953, when the cavity



Fig. 2. Case 1. October 14, 1953. Chest film after approximately two years, showing no change.

appeared, the sputa were also negative on culture for fungi, and bronchoscopy was essentially normal.

Figure 1 through 6 are films showing evolution and later filling of the cavity. Figure 1 shows extensive bilateral conglomerate silicosis. Figure 2 shows no essential change after approximately two years. Figure 3 shows a cavity with a fluid level at the right. Figure 4 shows partial filling of the cavity. Figure 5 shows complete filling of the cavity. Figure 6 shows no change after about one year.

Comment: This was a 56 year old hard coal miner with third-stage anthracosilicosis associated with pulmonary emphysema and cor pulmonale. He developed an asymptomatic cavity in one conglomerate mass which closed by filling.

Case 2. The patient, age 37, a white male hard coal miner for 12 years, was admitted here on two occasions, in 1950 and in 1951. He was hospitalized in 1950



Fig. 3. Case 1. October 26, 1953. Chest film showing large cavity with fluid level in the upper conglomerate nodule on the right side.

for acute appendicitis and an appendectomy was done. In 1951 he was readmitted because of fever, increased cough and expectoration, and gastrointestinal symptoms.

History indicated that he had had cough, expectoration, recurrent hemoptysis and exertional dyspnea for many years, and that he had been treated in a sanatorium for pulmonary tuberculosis although he never had positive tests for acid-fast bacilli. He ran a febrile course despite chemotherapy with various antibiotics, including streptomycin, and died about three weeks after hospitalization. Repeated sputa

smears were negative for acid-fast bacilli and negative on culture for fungi and K. pneumoniae.

Figures 7 and 8 are the chest films in this case, with figure 7 showing bilateral conglomerate nodules with a small cavity in the conglomerate nodule on the left, and figure 8 showing the cavity to be larger.

An autopsy showed anthracosilicosis with nontuberculous cavities in the conglomerate nodules of the upper lobes, one cavity being present on each side; the cavity on the left was larger than the one on the right. Bilateral pneumonia was found as well.

Comment: This patient had third-stage anthracosilicosis, with cavitation in both conglomerate masses. Prior to hospitalization here he had been treated for tuberculosis, despite the fact that tests for acid-fast bacilli were negative. Symptoms for many years were probably due to the nontuberculous cavities.

The autopsy disclosed bilateral cavitation, though the cavity on the right was not visualized by the chest film. The pneumonia which caused the patient's death may have been due to secondary infection from the cavities.

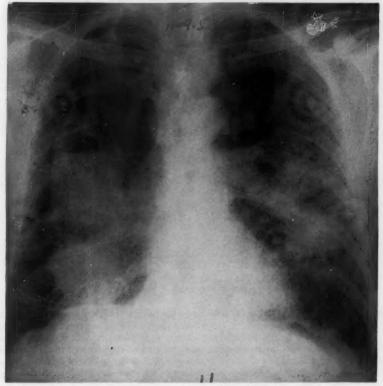


Fig. 4. Case 1. November 9, 1953. The chest film showing partial filling of the cavity.



Fig. 5. Case 1. November 30, 1953. Chest film showing complete filling of the cavity.

Case 3. The patient, age 62, a white male hard coal miner for 12 years, was admitted to this hospital on three occasions, in 1953, 1954 and 1955. The chief complaint was progressive dyspnea for about 10 years. In 1953 the diagnoses were third-stage anthracosilicosis with nontuberculous cavitation, and emphysema. In 1954 he was admitted for pneumothorax on the right, probably due to rupture of an emphysematous bleb. In 1955 hospitalization was precipitated by gastrointestinal bleeding, probably from a peptic ulcer. He died on the fourth day of hospitalization. Repeated sputa smears and cultures were negative for acid-fast bacilli.

Figures 9 through 11, the films in this case, show marked emphysema and bilateral marked conglomeration with a cavity in the left upper lobe which is larger in figure 10 and filled in figure 11. Pneumothorax is seen in figure 10, and its reabsorption in figure 11. Planigrams in 1954, not illustrated, showed cavities in both upper lobes.

An autopsy showed pulmonary emphysema and nontuberculous bilateral cavities in the conglomerate masses in the upper lobes. Figure 12, a photograph of the lungs, shows the bilateral cavities. In addition, a small gastric ulcer was found to account for the gastrointestinal bleeding. A terminal bilateral pneumonitis was also noted.

Comment: This was a 62 year old white male with third-stage anthracosilicosis, emphysema and bilateral nontuberculous cavities. Bleeding from a gastric ulcer apparently precipitated his death. Symptomatology, except terminally, was chiefly due to the pulmonary emphysema.

Case 4. The patient, age 66, a white male hard coal miner for about 40 years, was admitted to this hospital on five occasions, in 1951, 1952, 1953, 1954 and 1955.

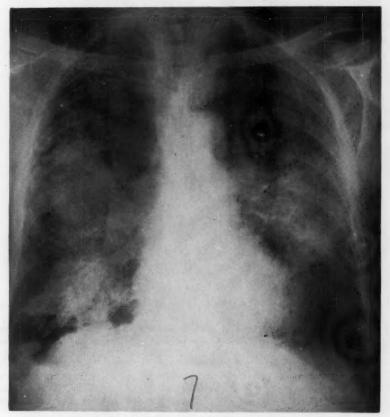


Fig. 6. Case 1. October 26, 1954. Chest film after approximately one year, showing no change in the conglomerate nodules on the right.

The chief complaint during all hospitalizations was progressive dyspnea. In 1951 he was considered to have third-stage anthracosilicosis, with nontuberculous cavitation and pulmonary emphysema. In the subsequent hospitalizations, cor pulmonale in failure was added to the above diagnoses. The patient died during his fifth hospitalization after having been here approximately four months. Repeated sputa smears and cultures were negative for acid-fast bacilli.

An autopsy showed pulmonary emphysema, and large anthracosilicotic masses

in both upper lobes containing multiple nontuberculous cavities bilaterally; on the left the cavitation was characterized by honeycombing. In addition, a terminal bronchopneumonia was found.

Comment: This was a 66 year old coal miner with third-stage anthracosilicosis, emphysema and multiple cavities, nontuberculous in etiology, and



Fig. 7. Case 2. December 12, 1950. Erect postero-anterior chest showing bilateral anthracosilicotic conglomerate nodules with a small cavity in the left conglomerate nodule.

right ventricular hypertrophy. Symptoms were chiefly due to pulmonary emphysema and cor pulmonale in failure.

Case 5. The patient, age 70, a white male hard coal miner for 38 years, was admitted February, 1956, with the chief complaint of shortness of breath which had been present for nine years. He was found to have third-stage anthracosilicosis with a nontuberculous cavity in the left upper lobe, emphysema and cor pulmonale in

failure. Sputa smears were negative for acid-fast bacilli. Despite therapy, he died about six weeks after hospitalization.

An autopsy showed anthracosilicosis, emphysema, right ventricular hypertrophy and large conglomerate nodules in both upper lobes, each containing multiple small, nontuberculous cavities.

Comment: This was a 70 year old white male with third-stage anthracosilicosis, emphysema, right heart failure and bilateral nontuberculous cavities. Symptoms were chiefly due to the pulmonary emphysema and corpulmonale in failure.

Case 6. The patient, age 61, a white male hard coal miner for 25 years, was hospitalized here on six occasions, in 1950, 1951, twice in 1952, 1953 and 1954. He died on the third day of the last hospitalization of bronchopneumonia, superimposed upon third-stage anthracosilicosis with bilateral upper lobe, nontuberculous cavities, bronchitis and emphysema. The symptomatology of all the hospitalizations was characterized by dyspnea, present for many years, fever, cough and expectoration; in

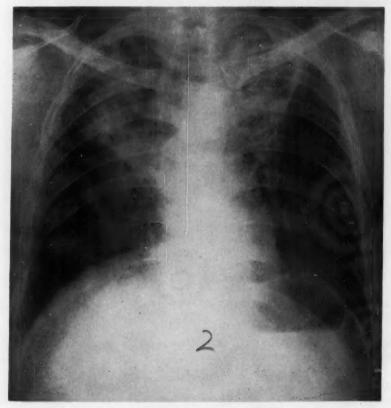


Fig. 8. Case 2. June 9, 1951. Chest film showing the cavity enlarged.



Fig. 9. Case 3. December 15, 1953. Erect postero-anterior chest film showing bilateral anthracosilicotic conglomerate nodules with a cavity and fluid level on the left and marked emphysema in the lower fields.

addition, hemoptysis was a symptom prior to the 1951 hospitalization. Repeated sputa smears and cultures during all hospitalizations were negative for acid-fast bacilli.

X-rays of the chest disclosed bilateral lobe conglomerate nodules with a cavity on each side, substantiated by planigrams; on occasion, the x-ray of the chest showed the cavities to be completely filled. Permission for autopsy was not granted.

Comment: This was a 61 year old white male, a hard coal miner for 25 years, with third-stage anthracosilicosis, whose chief complaints were referable to emphysema and recurrent attacks of acute bronchitis, though it was felt that the hemoptysis originated from the nontuberculous cavities.

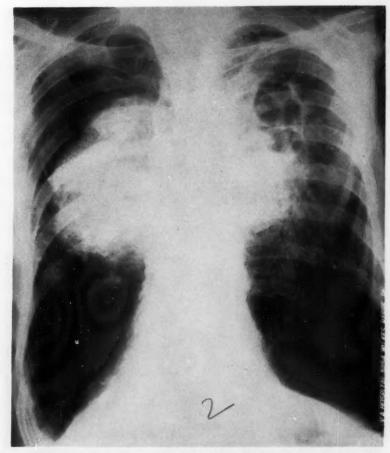


Fig. 10. Case 3. July 20, 1954. Chest film showing enlargement of the cavity and pneumothorax on the right.

He died from a bronchopneumonia probably secondary to the bronchitis and superimposed upon the chronic pulmonary disease.

Case 7. The patient, age 56, a white male hard coal miner for about 13 years, was admitted twice in 1955, complaining chiefly of exertional dyspnea, present for many years. During his first hospitalization he was considered to have third-stage anthracosilicosis with a nontuberculous cavity in the right upper lobe and emphysema. During his second hospitalization he was also felt to have cor pulmonale in failure. Repeated sputa smears and cultures were negative for acid-fast bacilli.

X-rays of the chest disclosed bilateral upper lobe conglomerate silicosis with a large cavity in the right upper lobe.

Comment: This was a 56 year old white male with third-stage anthracosilicosis, with a nontuberculous cavity in the right upper lobe, emphysema and cor pulmonale in failure. It was felt that the cavitary disease had produced few symptoms, his major disability being due to emphysema and cor pulmonale.

Case 8. The patient, age 56, a white male hard coal miner for about 20 years, was admitted in April, 1954, complaining of dyspnea on moderate exertion for about

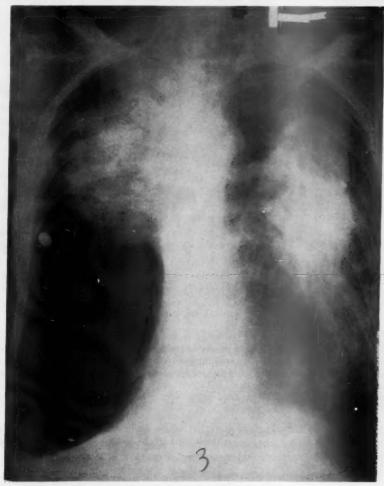


Fig. 11. Case 3. April 24, 1955. Chest film showing filling of the cavity and reëxpansion of the pneumothorax.

eight years. Ventilatory studies were normal. Repeated sputa smears and cultures

and gastric cultures were negative for acid-fast bacilli.

X-ray of the chest disclosed third-stage anthracosilicosis with conglomeration in the upper lobes; there was a suggestive cavity in the conglomerate mass in the left upper lobe. Planigrams of both upper lobes showed a moderate sized cavity in the left upper lobe.

Comment: This was a 56 year old white male with third-stage anthracosilicosis, with a nontuberculous cavity in the left upper lobe but without emphysema, as indicated by the pulmonary function tests. It was felt that few symptoms could be attributed to the cavity.

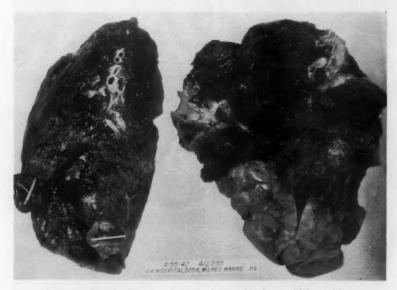


Fig. 12. Case 3. Photograph of the lungs, showing multiple cavities.

Case 9. The patient, age 55, a white male hard coal miner for about 20 years, was admitted in 1953 complaining chiefly of dyspnea on moderate exertion for about five years. X-ray of the chest showed third-stage anthracosilicosis with conglomerate nodules in both upper lobes; there was suggestive cavitation on both sides. Planigrams of both upper lobes revealed a large cavity on the right and two cavities of moderate size on the left. Repeated sputa smears and cultures were negative for acid-fast bacilli, as were cultures for fungi.

Comment: This was a 55 year old white male with third-stage anthracosilicosis and nontuberculous cavities in both upper lobes. It was felt that the patient had practically no symptoms referable to the cavities.

Case 10. The patient, age 57, a white male hard coal miner for 17 years, was admitted in 1955 complaining chiefly of progressive exertional dyspnea during the last five years. He was considered to have third-stage anthracosilicosis with a non-

tuberculous cavity in the left upper lobe, emphysema and cor pulmonale in failure. Repeated sputa smears and cultures and gastric cultures were negative for acid-fast bacilli; the sputum was also negative for fungi on culture. Bronchoscopy showed normal findings, with the bronchoscopic smear negative for acid-fast bacilli. X-ray of the chest showed silicosis, with conglomeration in both upper lobes and a suggestive cavity in the left upper lobe; planigrams of both upper lobes revealed a moderate sized cavity in the left upper lobe.

Comment: This was a 57 year old white male hard coal miner with third-stage anthracosilicosis and nontuberculous cavitation, pulmonary emphysema and cor pulmonale in failure. Symptoms were chiefly referable to the emphysema and cor pulmonale in failure.

DISCUSSION

Silicosis has been defined as a pneumoconiosis due to the inhalation of silica, while anthracosilicosis has been similarly defined as due to the inhalation of a mixture of silica and carbon. In this report these terms are used interchangeably, since the course of both diseases seems to be quite similar. On the basis of the chest x-ray, silicosis has been divided into three stages: 1 The first stage is characterized by an increase in the linear markings and in the density and width of the hilar shadows; the second, by nodulation and intensification of the abnormal linear shadows; the third, by the appearance of large conglomerate nodules or masses. The abnormalities on the chest x-ray reflect the reactive fibrosis caused by silica, which has been described by Mayer and Rappaport.2 Corresponding to the first stage is the fibrotic reaction in the perivascular and peribronchial lymph channels and draining hilar glands. The second stage becomes manifest with the continuation of the fibrotic reaction, until intensification of the linear shadows and nodulation occur. With conglomeration due to coalescence of silicotic nodules over large areas, the third stage is seen. Difference of opinion exists, however, as to the exact nature of the conglomerate nodule. That it is all a reactive fibrosis to silica is a possibility. Gardner 8 and Harrison 4 state that over 50% of the conglomerate masses, examined histologically, are complicated by tuberculosis. Gardner 8 also believes that, because of the inhalation of coal as well as silica, the anthracosilicosis of the hard coal miner is more apt to manifest itself as massive conglomerate nodules than is the silicosis incurred by exposure to silica alone, as in sandblasting. Costero 5 believes that all the lesions of silicosis, not only those of the third stage, are influenced by infection, particularly tuberculosis.

It is generally accepted that tuberculosis is the most common cause of pulmonary cavitation. That tuberculosis is a frequent occurrence in third-stage silicosis is evident when one considers that over 50% of the conglomerate masses are said to be infected with tuberculosis. Thus, when cavitation occurs in a conglomerate mass, it is usually presumed to be of tuberculous nature. However, the occurrence of nontuberculous cavitation

must not be overlooked. Gardner ⁶ in 1939 reported the presence of non-tuberculous cavities in areas of massive fibrosis. Noting that the blood vessels supplying these masses were practically all obliterated, he ventured the opinion that the cavitation was of ischemic origin. Vorwald ⁷ and Geever ⁸ were of the same opinion, with the former also suggesting the toxic action of high concentrations of silica in the conglomerate mass as a cause of nontuberculous cavitation. In addition, Rubin ⁹ mentions both non-tuberculous infection and ischemia, acting synergistically, as within the realm of etiologic possibilities.

Aside from the problem of etiology, other writers have stressed the occurrence of nontuberculous cavitation in third-stage anthracosilicosis, among them being Mariani ¹⁰ and Nathanson and Morganstern, ¹¹ who reported cases with such pathology. In addition, Wall ¹² presented 100 cases of anthracosilicosis in all stages who came to autopsy. He found 15% with nontuberculous cavitation, with only 3% associated with tuberculosis. His percentage of nontuberculous cavitation is much higher than ours—15% as against approximately 1%—while his incidence of tuberculous infection was similar to ours—3% as against approximately 2% in our series.

Differentiation between tuberculous and ischemic cavities in third-stage anthracosilicosis is of the utmost importance, since the diagnosis of tuberculosis, in addition to the stigma it unfortunately carries, the financial hardship it imposes, and the anguish it causes both patient and family, entails prolonged hospitalization and probably more prolonged antituberculous chemotherapy.

In our 10 cases with nontuberculous cavitation, the symptomatology as well as the mortality was chiefly due, not to the cavitation, but to the complicating emphysema and/or cor pulmonale in failure. We would like to call attention in particular to case 1. It is unique in that the x-rays show evolution of an ischemic cavity and its subsequent closure by filling. On the basis of our cases, we would venture to say that it is the large conglomerate mass which is particularly susceptible to ischemic necrosis resulting in cavitation. This breakdown of a conglomerate mass may be compared to the necrosis of a tumor which has outgrown its blood supply.

SUMMARY

1. Ten cases of third-stage anthracosilicosis with nontuberculous ischemic cavities have been presented. Four of the 10 cases were proved by autopsy to have nontuberculous cavities, while the other six were considered nontuberculous on bacteriologic evidence.

2. In this series of approximately 1,200 cases of anthracosilicosis in all stages, the incidence of nontuberculous cavitation was approximately 1%, as compared to approximately 2% with tuberculous infection.

3. In the 10 cases with nontuberculous cavitation, the symptomatology

and the mortality were chiefly due, not to the cavitation, but to the complicating emphysema and/or cor pulmonale in failure.

4. Even though its incidence is low, the occurrence of nontuberculous cavitation in third-stage anthracosilicosis should be recognized.

SUMMARIO IN INTERLINGUA

Iste articulo sublinea le facto que cavitationes pulmonar es non semper e non necessarimente de natura tuberculotic e que il occurre casos de cavitation ischemic—probabilemente de natura degenerative—in massas conglomerate de anthracosilicosis del tertie stadio. Es presentate 10 tal casos con cavitation nontuberculotic. In le curso de circa cinque annos e medie, approximativemente 1.200 casos de anthracosilicosis in omne stadios esseva vidite a iste hospital. Le serie includeva 24 casos complicate per tuberculose—un incidentia de 2%—e 10 casos con cavitation nontuberculotic—un incidentia de circa 1%. Le differentiation clinic inter iste duo gruppos—le gruppo tuberculotic e le gruppo nontuberculotic—esseva facite super le base de repetite examinationes bacteriologic. In quatro del 10 casos de cavitation nontuberculotic, provas additional del natura nontuberculotic del cavitation esseva obtenite in le constatationes post morte—tanto grossier como etiam microscopic.

Il es generalemente acceptate que tuberculose es le plus commun causa de cavitation pulmonar e que tuberculose es un occurrentia frequente in silicosis del tertie stadio. Tamen, on non debe negliger le facto que il occurre etiam cavitationes nontuberculotic. Inter le causas nontuberculotic, anthracosilicosis occupa un rango prominente. In nostre 10 casos de cavitation nontuberculotic, le symptomatologia e etiam le mortalitate resultava primarimente non del cavitation sed del usual complicationes de chronic morbo thoracic—i.e. emphysema, infection, corde pulmonal con disfallimento, etc. Super le base de nostre casos nos risca postular que il es le grande massa conglomerate que es particularmente susceptibile a disveloppar le necrosis ischemic resultante in cavitation.

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MODIFICATION OF ABNORMAL SERUM LIPID PATTERNS IN ATHEROSCLEROSIS BY AD-MINISTRATION OF SITOSTEROL*

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The reports by Peterson that the addition of soybean sterols to experimental diets of chicks appeared to inhibit the absorption of cholesterol ¹ and to effect a decreased incidence of atherosclerosis ² have stimulated study of the effects of ingestion of various plant sterols.

The presence in higher plants of sterols (phytosterols) which are closely related to cholesterol has long been recognized. The most widely distributed of the phytosterols are the sitosterols, of which there are at least five. Gamma sitosterol is the principal sterol of soybean oil, and presumably the active component of the sterol mixture employed by Peterson. Studies in our laboratory have been concerned largely with beta sitosterol, a stereo-isomer of the gamma sterol, differing from it only in the configuration on the carbon-24 atom of the side chain. Beta sitosterol is the chief sterol of tall oil and of cottonseed oil.

Beta and gamma sitosterols are closely related in chemical structure to cholesterol (figure 1). They have the same tetracyclic nucleus found in cholesterol, and differ only in the carbon-17 side chain. Despite this similarity in the chemical structure of sitosterol and cholesterol, there is a marked difference in their absorbability from the intestinal tract, sitosterol being relatively nonabsorbable.

The inhibitory effect of sitosterol on cholesterol absorption is illustrated in figure 2, which summarizes the results of adding cholesterol and cholesterol-plus-sitosterol to the diet of albino rats. The addition of 1% cholesterol results in a modest increase in serum cholesterol and a marked increase in hepatic cholesterol. The further addition of 5% beta sitosterol to the high cholesterol diet completely prevents this accumulation of cholesterol in serum and liver. Although the administration of cholesterol readily causes a rise in liver cholesterol, the rat is particularly resistant to the development of hypercholesterolemia and atherosclerosis.³ To produce even a modest increase in serum cholesterol with cholesterol feeding, the animals used in

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^{*} Presented at the Thirty-seventh Annual Session of The American College of Physicians, Los Angeles, California, April 17, 1956.

[†] With the technical assistance of Joan D. Wathen, B.S., and Ursula Jegher.

This investigation was supported by research grants from Eli Lilly & Co., Indianapolis, Indiana, and the Commonwealth of Kentucky Medical Research Commission.

this experiment had been subjected to prior radiation destruction of the thyroid by iodine¹⁸¹.

In contradistinction to the rat, the rabbit readily develops a pronounced hypercholesterolemia when fed a diet containing 1% cholesterol and 5% cottonseed oil. The effects in rabbits of such a diet, with and without the further addition of 5% sitosterol, are shown in figure 3. In similar studies continued over a longer period of time, Pollak demonstrated, in addition to this effect on serum cholesterol, a reduced incidence of cholesterol atherosclerosis.⁴

The effectiveness of sitosterol in blocking the absorption of cholesterol in experimental animals prompted its study in man as a possible means of

Fig. 1. Structural formulae of cholesterol and beta sitosterol. Sitosterol differs from cholesterol only in the presence of an ethyl group (indicated by arrow) on carbon-24.

achieving a reduction in serum cholesterol. Sitosterol has been administered to 24 patients for sufficient periods of time to evaluate its effect on serum cholesterol and other lipids. Several types of sitosterol suspensions were employed in early studies, but during the last 18 months a 20% suspension of sitosterols, predominantly beta, has been used.*

Six to 8 gm. of sitosterol were administered orally immediately before the ingestion of food, the usual total being 18 to 25 gm. per day. There was no restriction as to type or amount of diet. Because of the recognized variability of serum cholesterol levels, a number of control determinations

^{*} Cytellin, Eli Lilly & Co., Indianapolis, Indiana.

EFFECT OF FEEDING CHOLESTEROL AND CHOLESTEROL + SITOSTEROL TO THE HYPOTHYROID RAT

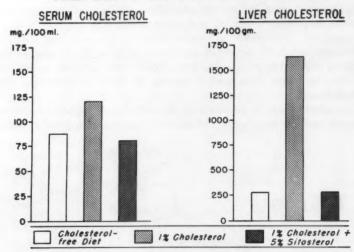


Fig. 2. Interference by sitosterol with cholesterol absorption in the rat. The values shown are the means of groups of five animals. Liver cholesterol is expressed as mg./100 gm. liver (wet weight).

EFFECT OF FEEDING CHOLESTEROL AND CHOLESTEROL + SITOSTEROL TO THE RABBIT

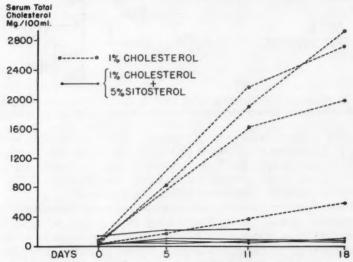


Fig. 3. Prevention by sitosterol of hypercholesterolemia in the cholesterol-fed rabbit.

TABLE 1
Diagnostic Classification of the 24 Patients

Occlusive vascular disease:	
Previous myocardial infarction (3 of these also had hypothyroidism) (1 of these also had xanthelasma)	11
Peripheral arterial disease	3
Secondary hypercholesteremia:	
Hypothyroidism (3 of these also had myocardial infarction)	5
Renal disease	3
Xanthomata: Xanthelasma (1 of these also had myocardial infarction)	2
Essential (familial) hyperlipemia with xanthomata	4

were made on each patient, during periods both of placebo administration and of no medication. Details of the method of study and of the laboratory technics employed have been previously published.^{5, 6}

Included in the study were patients with a variety of diagnoses, including coronary and peripheral arterial disease, hypothyroidism, familial hyperlipemia with xanthomatosis and hypercholesterolemia secondary to renal disease (table 1). The largest single group was the 11 patients with prior myocardial infarction, the diagnosis in each case being on the basis of both the clinical picture and the electrocardiogram.

42 YEAR OLD MALE - POST MYOCARDIAL INFARCTION SERUM CHOLESTEROL CHANGES DURING 30-MONTHS OBSERVATION

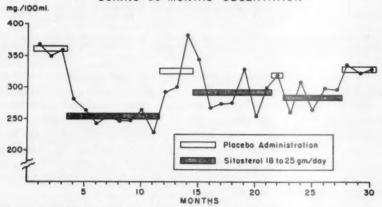


Fig. 4. The effect of sitosterol on serum cholesterol of Mr. M. G. The points plotted indicate the mean of the several serum cholesterol determinations performed each month. The bars represent the mean serum cholesterol level for each of the four placebo and three sitosterol periods.

One such patient, Mr. M. G., a 42 year old power shovel operator, was admitted to the Louisville General Hospital with a history of crushing substernal pain, apprehension, dyspnea and profuse perspiration, which came on while he was at work. Serial electrocardiograms showed the classic changes associated with acute anterior wall myocardial infarction. Treatment consisted of bed-rest, sedation, oxygen and Dicumarol anticoagulation. Recovery was uneventful. The patient was discharged from the hospital at six weeks, returned to work approximately four months after his infarction, and has continued to work as a power equipment operator. Periodic determinations of serum cholesterol and other lipids were begun at the time of discharge from the hospital and have been continued for the subsequent two and one-half years. Figure 4 summarizes the effects on serum cholesterol of repeated administration of sitosterol.

TABLE 2
Mean Control and Sitosterol Treatment Levels of Serum Lipids

Diagnosis	Control			Sitosterol				
	No. Mos.	Total Cholesterol	Lipid Phosphorus	Total Lipid	No. Mos.	Total Cholesterol	Lipid Phosphorus	Total Lipid
PAD	4	266 (11)	13 (1.8)	884 (58)	28	230 (15)	13 (1.3)	736 (68)
PAD	3	606 (47)	23 (3.5)	1.895 (367)	13	540 (138)	22 (5.3)	1,708 (497)
PAD	2	276 (5)	15 (0.4)	1.072 (41)	13	234 (14)	13 (1.4)	967 (41)
CAD	2	293 (16)	16 (1.6)	930 (29)	29	240 (14)	13 (1.0)	715 (72)
CAD	8	338 (33)	16 (1.7)	1,137 (17)	20	273 (29)	15 (1.7)	940 (172)
CAD	3	323 (12)	15 (1.6)	1,006 (47)	25	289 (16)	14 (1.0)	885 (53)
CAD	3	494 (29)	16 (1.0)	1,280 (135)	3	413 (45)	15 (1.0)	1,017 (86)
CAD	6	286 (11)	12 (1.3)	942 (115)	8	243 (10)	12 (1.7)	835 (21)
CAD	2	261 (3)	13 (1.0)	916 (11)	3	227 (12)	11 (0.7)	823 (35)
CAD	2	266 (2)	16 (1.0)	806 (51)	15	245 (16)	13 (1.6)	732 (67)
CAD&X1	2	263 (4)	12 (1.4)	792 (11)	17	237 (16)	12 (1.0)	673 (60)
CAD&Mx	3	340 (75)	13 (1.2)	881 (103)	1	175 (5)	9 (1.0)	538 (15)
CAD&Mx	3	285 (11)	14 (1.4)	937 (95)	2	214 (8)	11 (0.9)	663 (3)
CAD&Mx	3	365 (42)	17 (1.4)	1,039 (99)	9	294 (29)	14 (1.7)	826 (97)
Mx	7	313 (22)	14 (1.0)	850 (90)	9 8	268 (14) 215 (20)	12 (1.5) 11 (0.8)	744 (86) 671 (51)
Mx	9	246 (26)	11 (0.9) 15 (1.4)	772 (57)	14	212 (21)	12 (1.6)	0/1 (31)
Ren	/	242 (26) 340 (64)	12 (1.4)	1.093 (258)	3	253 (66)	12 (1.7)	1.019 (424)
Ren Ren	10	340 (64) 549 (213)	21 (5.2)		10	489 (111)	21 (3.9)	1,960 (895)
Ken K1		299 (16)	16 (1.4)	2,161 (1,052) 908 (61)	15	264 (17)	14 (1.4)	822 (97)
EH	3	390 (20)	15 (1.7)	1.124 (128)	5	363 (13)	13 (2.6)	1.188 (35)
EH	3	798 (44)	24 (5,8)	2,280 (213)	5	790 (43)	22 (1.4)	2,246 (109)
EH	6	778 (114)	32 (3.6)	3.815 (854)	19	540 (138)	26 (5.8)	2,797 (802)
EH	7	288 (127)	15 (3.6)	1,984 (931)	20	277 (104)	15 (3.4)	1,670 (924)

The values are expressed in mg./100 ml. of serum, followed by the standard deviations in parentheses. Key to diagnosis: CAD—myocardial infarction; PAD—peripheral arterial insufficiency; Mx—hypothyroidism; Reneral disease; X1—xanthelasma; EH—hyperlipemia with xanthomata.

The mean serum cholesterol, total lipid, and lipid phosphorus levels for each of the 24 patients during control and sitosterol period are tabulated in table 2. Inspection of the data reveals a rather consistent reduction of serum cholesterol during the periods of sitosterol administration. This effect is graphically illustrated in figure 5, in which the per cent change from mean control level of serum cholesterol is plotted for each of the 24 patients. It is seen that the administration of beta sitosterol is accompanied by a fall in serum cholesterol which is manifest during the first month and sustained throughout the period of study.

A reduction not only of serum cholesterol but also of phospholipid and total lipid was observed with sitosterol administration (table 2.) The mean change in serum total cholesterol, phospholipid and total lipid for the

entire group of 24 patients is depicted in figure 6. The mean reduction of serum cholesterol was 15.5%, of phospholipid, 9.4%; and of total lipid, 13.8%. The somewhat greater fall in cholesterol than in phospholipid results in a slight reduction of the total cholesterol/phospholipid ratio.

Although the number of patients in the individual disease categories is small, inspection of figure 7 suggests that there is some relationship between the etiology of hypercholesterolemia and the response to sitosterol. Thus it will be noted that, as a group, the patients with myxedema demonstrate

EFFECT OF SITOSTEROL ON SERUM CHOLESTEROL (24 PATIENTS) (24 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (29 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (29 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATIENTS) (27 PATIENTS) (28 PATIENTS) (29 PATIENTS) (20 PATIENTS) (21 PATIENTS) (22 PATIENTS) (23 PATIENTS) (24 PATIENTS) (25 PATIENTS) (25 PATIENTS) (26 PATIENTS) (27 PATI

Fig. 5. Effect of sitosterol on serum cholesterol of 24 patients. The points represent the mean of the several cholesterol determinations performed each month, and are expressed as per cent deviation from the mean control value of that patient. The mean control level is indicated by the horizontal broken line; the solid line indicates the mean effect of sitosterol. The patients with essential hyperlipemia are represented by triangles, and those with hypercholesterolemia secondary to renal disease by crosses. The greater variability of serum cholesterol levels during both control and sitosterol periods of these patients is apparent.

the greatest reduction in serum cholesterol. It has been suggested that this is a consequence of the low turnover rate of cholesterol in hypothyroidism, which serves to accentuate the effect on serum levels of any change in the amount of cholesterol absorbed. The patients with familial or essential hyperlipemia are the other group which deserve comment. The wide fluctuations in serum cholesterol during both control and treatment periods in these patients make evaluation of the results difficult, but it appears that sitosterol exerts less influence in this group than in the usual hypercholesterolemic patient.

In seven of the 24 patients serial ultracentrifugal analysis of serum lipoproteins was made during both control and sitosterol periods. A trend toward lower levels of Sf 3–100 lipoproteins was observed during the administration of sitosterol, but this effect was less consistent than was the reduction of serum cholesterol and total lipid.⁶

The reduction in serum cholesterol and other lipids produced by sitosterol can best be explained on the basis of its interference with absorption of cholesterol from the digestive tract. This effect is not necessarily identical with that of dietary restriction of cholesterol, since sitosterol might be expected to reduce absorption of cholesterol present in the bile as well as that present in the diet.

EFFECT OF SITOSTEROL ON SERUM CHOLESTEROL AND OTHER LIPIDS (MEAN 24 PATIENTS)

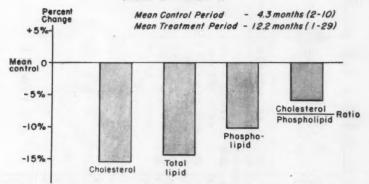


Fig. 6. Mean reduction of serum cholesterol and other lipids. The mean effect on 24 patients of 18 to 25 gm. of sitosterol per day without dietary restriction is expressed as per cent change from mean control levels.

That sitosterol does interfere with the absorption of cholesterol from the gut has been confirmed by Hernandez, using C¹⁴ labeled cholesterol.⁸ Two mechanisms of this interference with absorption have been proposed. Davis has demonstrated that, under suitable conditions, cholesterol and sitosterol will form a mixed crystal which is much less soluble than either of the sterols alone, and he has suggested that sitosterol may act by combining with cholesterol in the gastrointestinal tract to form such crystals, thus binding the cholesterol and preventing its absorption.⁹ An alternative suggestion is that sitosterol competes with cholesterol for esterification, a step in the transport mechanism by which cholesterol is absorbed.⁶

Any attempt to evaluate the clinical efficacy of sitosterol in the management of atherosclerosis is beset by many difficulties. There are no available criteria for accurate assessment of the degree of atherosclerosis in the living

patient. It is only when atherosclerosis has progressed to a point where there is significant interference with blood flow that it is clinically manifest. Even these late complications of atherosclerosis are a poor index of the extent of the disease, since they are dependent also upon the location of the atheromata. Extensive atherosclerosis of the aorta may defy detection, while a single plaque strategically placed in a coronary artery may lead to myocardial infarction and death. Despite these discrepancies between the degree of atherosclerosis and the occurrence of myocardial infarction, it is this group of patients that would seem to offer the best opportunity to evaluate agents of possible value in the treatment of atherosclerosis.

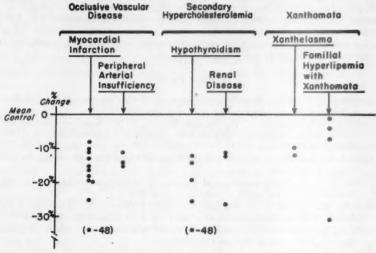


Fig. 7. Reduction in serum cholesterol by sitosterol in the various disease categories. The mean reduction of serum cholesterol expressed as per cent change from control level, for each of the 24 patients is indicated. Four patients appear twice, due to multiple diagnoses (table 1).

Our observations to date are insufficient to draw conclusions regarding the effect of sitosterol on atherosclerosis. Of the 11 patients with myocardial infarction who have been treated, one died of myocardial infarction (his third) after three months of sitosterol administration. The remaining 10 have been treated for periods of up to 29 months (mean, 15.8 months). There have been no recurrent infarctions in this group, and no toxic manifestations attributable to sitosterol.

SUMMARY

In experimental animals fed a high cholesterol diet the plant sterol, beta sitosterol, interferes with the absorption of cholesterol and prevents its accumulation in serum and liver.

The prolonged administration to man of sitosterol in the daily dosage of 18 to 25 gm. results in a sustained reduction of serum cholesterol. In the 24 patients treated, the mean decrease in serum cholesterol was 15.5% of the control level.

The absence of toxic effects permits further study of the possible therapeutic value of sitosterol in human atherosclerosis.

SUMMARIO IN INTERLINGUA

In animales experimental a dieta ric in cholesterol, le sterol vegetal sitosterol beta inhibi le absorption de cholesterol e preveni su accumulation in sero e hepate.

Le prolongate administration de sitosterol a humanos in dosages diurne de 18 a 25 g resulta in un persistente reduction del cholesterol seral. In un gruppo de 24 patientes assi tractate, le reduction medie del cholesterol seral amontava a 15,5% del nivello de controlo.

Le absentia de effectos toxic permitte studios additional del possibile valor therapeutic de sitosterol in atherosclerosis human.

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CUTANEOUS LEISHMANIASIS: A REPORT OF 10 CASES *

By PER H. LANGSJOEN, Captain (MC), USA, Cristobal, Canal Zone

THE fact that ever-increasing numbers of people are becoming 20th Century Marco Polos is rapidly making medical provincialism an undesirable characteristic. The widespread travels of our citizens, particularly those in military service, have made such illnesses as malaria, coccidioidomycosis, acute hemorrhagic fever, schistosomiasis, Japanese B encephalitis and leptospirosis very real to the medical profession in all corners of the United States. Among these diseases, leishmaniasis demands inclusion.

It is the purpose of this paper to present 10 cases in young white American soldiers of cutaneous leishmaniasis contracted in the area near Camp Pina in the Panama Canal Zone, with the results of their observation and study.

Cutaneous leishmaniasis is neither a new nor a rare disease in Panama. Since the first case was reported by Darling in 1910 it has been quite frequently seen and often reported. Calero and Johnson in 1953 collected 32 cases of pathologically proved leishmaniasis from the literature and added seven of their own. They pointed out that it was largely a rural disease, especially prevalent in those people who worked or lived in virgin timber areas. In checking the origins of their cases they were easily able to find considerable numbers of people with the scars of what appeared to be healed lesions. They concluded that the true incidence among the population of the Republic of Panama undoubtedly was considerably higher than the reported incidence. Indeed, it is not difficult to perceive that the people most apt to be infected in this area would be the ones least apt to be cared for in major medical installations.

CASE REPORTS

Case 1. An 18 year old white Army private (first class) was admitted to this hospital on April 11, 1955.

On approximately March 1, 1955, he had noted the appearance of an itching papule on the dorsum of the left second finger which formed a pustule and ulcerated in about one week. On about April 4 he became aware of a swelling on the inner aspect of the left elbow. In spite of treatment with systemic penicillin, Aureomycin and various local ointments, his ulcer gradually progressed in size.

He had been at Camp Pina from December 28, 1954, to March 5, 1955. He had been on night jungle maneuvers in late February and early March. He wore no mosquito gloves, and always slept on his back with both hands over his head.

* Received for publication March 5, 1956.
From the Health Bureau, Canal Zone Government.
All cases studied at Coco Solo Hospital, Cristobal, Canal Zone.
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Physical examination on admission revealed an oval 2 cm. ulcer on the dorsum of the left second finger, with a necrotic base and a raised, dull red border. There was a string of enlarged subcutaneous nodules from the left epitrochlear region to the axilla, with nontender left axillary node enlargement.

Basic laboratory studies, including hemoglobin, white cell count and differential, sedimentation rate, PPD #1, serum bilirubin, serum albumin and globulin, chest x-ray and Bromsulphalein retention, were negative or normal.

The diagnosis of cutaneous leishmaniasis was made on the basis of a compatible

biopsy from the edge of the ulcer.

He received 35 c.c. of Fuadin intramuscularly from April 16 to 25, and a second 35 c.c. from May 2 to 9, with apparent complete healing of the ulcer and disappearance of the nodules in the upper arm, and a 70% reduction in the size of the axillary nodes. He suffered mild arthralgia during the last two days of the second course.

In mid-June, 1955, he noted the appearance of a small papule at the border of the scar which in the following four months very gradually increased in size. He was eventually rehospitalized with a 0.5 cm., dull red papule with an ulcerated center. This yielded very infrequent organisms on smear, and responded satisfactorily to two subsequent courses of Fuadin.

Case 2. An 18 year old white male Army private was admitted to this hospital on April 19, 1955.

He had noted the appearance of two itchy papules on the dorsum of the left wrist on about April 1, 1955, which ulcerated in about one week and gradually increased in size in spite of systemic penicillin and Aureomycin ointment.

He had been at Camp Pina from December 10, 1954, to March 5, 1955, and had been on night jungle maneuvers in late February and early March. He had no consistent sleeping habits.

Physical examination revealed two 1.5 cm. oval ulcers on the dorsum of the left wrist, with necrotic bases and raised dull red borders, with a 2 cm. left axillary node.

Basic laboratory work gave entirely normal results.

The diagnosis was made on the basis of a positive biopsy from the border of one of the lesions.

He received 35 c.c. of Fuadin from April 26, 1955, to May 3, 1955, and a second 35 c.c. from May 11 to May 17, 1955, with complete healing by May 23. Moderate arthralgia was noted the last two days of the second course.

Case 3. A 22 year old white male Army private was admitted on April 25, 1955. About March 1 he had noted the appearance of five itching papules on the dorsum of the right wrist and lower forearm which became ulcers in about one week. About April 1 he noted the appearance of two similar lesions on the left side of his neck. All these lesions progressed in size in spite of various local applications.

He had been in Camp Pina from February 1, 1955, to March 10, 1955. He was on night jungle maneuvers in late February and early March. He had no consistent sleeping habits, and always used mosquito helmet and gloves. However, he had been issued two left gloves, with the result that the use of the left glove on the right hand afforded incomplete protection.

Physical examination revealed five 0.5 cm. crusted lesions on the dorsum of the right wrist, with raised, dull red borders, and two 0.3 cm. similar lesions on the left side of the neck. He had a string of nontender subcutaneous nodules extending from the right epitrochlear region to the axilla.

Basic laboratory studies gave normal results except for a doubtful positive serologic test for syphilis.

The diagnosis was made on the basis of a positive biopsy from the border of one of the ulcers.

He received 35 c.c. of Fuadin from May 2 to May 9, and a second 35 c.c. from May 17 to May 24. He suffered from moderate arthralgia during the last day of the first course and the last two days of the second course.

His lesions appeared healed by May 27.

Case 4. A 29 year old white male Army private (first class) was admitted on May 3, 1955.

About April 12 he had noted the appearance of an itchy papule on the ventral aspect of each lower forearm which formed ulcers in about one week and became progressively larger in spite of systemic penicillin and Furacin applications.

He had been at Camp Pina from January 15, 1955, to March 25, 1955, and had been on night jungle maneuvers in late February and early March. He always slept on his back with both hands under his head, and recalled many insect bites about the wrists after sleeping in the jungles.

Physical examination revealed 2 cm. oval ulcers on the ventral aspect of each wrist with necrotic bases and raised, dull red borders, and a string of beadlike, nontender subcutaneous nodules extending up the right arm to the epitrochlear region.

Basic laboratory tests yielded normal results.

The diagnosis was made from positive smears of scrapings from the borders of the ulcers.

He received 35 c.c. of Fuadin from May 5 to May 13, and a second 35 c.c. from May 20 to May 27. He experienced moderately severe arthralgia in the last two days of the first course and the last three days of the second.

His lesions appeared healed on May 31 and he was discharged on June 1. On about July 7, 1955, doughnut-shaped lesions recurred which increased in severity in spite of two weeks of antibiotic treatment and local applications. Smears were positive for leishmania. He was rehospitalized on July 26 and received 50 c.c. of Fuadin from July 26 to August 4, and 35 c.c. from August 12 to 18. Moderately severe arthralgia again was noted. Complete healing resulted.

Case 5. A 25 year old white male Army corporal was admitted on May 3, 1955. About April 15 he had noted the appearance of a papule on the dorsum of the left wrist which ulcerated and became gradually larger in spite of the application of various ointments.

He had been at Camp Pina from January 21, 1955, to March 5, 1955, and had been on night jungle maneuvers only on March 3 and 4. He had worn mosquito helmet and gloves on that occasion. He always slept on his right side with both hands under his head, and recalled many insect bites, particularly on the left wrist, the night in the jungle.

Physical examination revealed an oval 2 cm. ulcer on the dorsum of the left wrist with a necrotic base and raised, dull red border, and a string of nontender, beadlike subcutaneous nodules extending from the lesion into the axilla, with a 3 cm. left axillary node.

Basic laboratory studies gave entirely normal results.

The diagnosis was made from the finding of the organism on slides of scrapings from the border of the ulcer, as well as in sections of a biopsy of one of the subcutaneous nodules.

He received 35 c.c. of Fuadin from May 6 to May 13, and a second 35 c.c. from May 21 to May 27. He suffered from moderate arthralgia during the last three days of each course. The ulcer appeared healed by about May 31, and the nodules all disappeared.

Case 6. A 21 year old white Army corporal was admitted on May 4, 1955.

On about March 25 he had noted two itchy papules on the ventral aspect of the right wrist which ulcerated on about April 6. On about that date he noted the

appearance of a similar lesion in the right popliteal fossa. He had received no treatment.

He had been at Camp Pina from January 21 to March 9, and had been on night jungle maneuvers in late January and early February and in the first week in March. He wore mosquito helmet and gloves, and always slept with the right arm extended up over his head. On the night of March 3 he was so indiscreet as to make his bed atop an ant hill, a fact he became painfully aware of during the night. He removed his trousers and for about one hour was without pants in the jungle while he tried to get the ants out of his trousers.

Physical examination revealed two 1 cm. ulcers on the lateral aspect of the right wrist, with necrotic bases and red raised borders, and with a beadlike string of subcutaneous nodules extending up the right arm into the axilla, where there were three enlarged nodes. He also had a similar ulcer, about 0.5 cm. in diameter, in the right popliteal fossa.

Basic laboratory studies yielded negative results.

The diagnosis was made from positive scrapings from the ulcer borders and appearance of the organism in section of one of the subcutaneous nodules.

He received 35 c.c. of Fuadin from May 6 to May 13, and a second 35 c.c. from May 21 to May 28. He had mild arthralgia from May 26 to May 28. The lesions appeared healed and the nodules gone by May 31.

Case 7. A 21 year old white male Army private (first class) was admitted on May 10, 1955.

About March 15 he had noted the appearance of a papule behind the left ear which ulcerated and increased in size despite local applications.

He had been at Camp Pina from January 28 to March 6, and had made only unofficial excursions into the jungle.

Physical examination on admission revealed a 1.5 cm. crusted oval ulcer behind the left ear with a raised, dull red border.

Basic laboratory studies gave normal results.

The diagnosis was made on the basis of positive scrapings from the borders of the ulcer.

He received 35 c.c. of Fuadin from May 11 to May 18, without clinical side reactions. His lesion appeared healed by May 27.

Case 8. A 18 year old white male Army private (first class) was admitted on May 18, 1955.

On about March 1, 1955, he had noted the appearance of three itchy papules on the dorsum of the left hand and two on the right eyebrow which ulcerated in about 10 days. In spite of local applications the lesions gradually increased in size.

He had been at Camp Pina intermittently from October, 1954, to May 7, 1955, but had been on night maneuvers in the jungle only during the first weeks of October, February and March. He disdained the use of gloves and head nets, and always slept on his stomach.

Physical examination on admission revealed a 1 cm. crusted ulcer with raised red border, and two 0.5 cm. similar lesions on the dorsum of the left hand, plus two 0.75 cm. similar lesions on the right eyebrow and eyelid. There was a nontender, enlarged right preauricular node.

Basic laboratory studies yielded normal results.

The diagnosis was made on the basis of positive scrapings of the ulcer borders. He received 35 c.c. of Fuadin from May 19 to May 26, without untoward symptoms and with apparent healing by June 3. However, on about July 10, 1955, he noted the appearance of a small red papule at the border of the scar of one of the ulcers on his eyebrow. In the following three months this increased very slowly in

size until it measured about 0.4 cm. and eventually ulcerated. Scrapings showed infrequent organisms, and from September 23 to October 4 he received 50 c.c. of Fuadin, without clinical toxicity and with complete healing.

Case 9. A 21 year old white male soldier was admitted to the Surgical Service on April 16, 1955, because of a fractured right clavicle.

On approximately April 25 he had become aware of a small ulcer on the posterior aspect of the right middle lower leg and one on the left midpretibial region which gradually increased in size.

He had been at Camp Pina from January 28 to April 1, and had been on night jungle maneuvers in late February and early March. He always wore gloves and head nets, but had the unsoldierly habit of "unblousing" his trousers, leaving exposed skin between the bottom of his trousers and the boot tops.

Examination revealed a 1.5 cm. ulcer on the back of the right lower leg and a 2.5 cm. ulcer in the left midpretibial region.

Routine laboratory studies gave normal findings.

The diagnosis was made on the basis of positive scrapings from the ulcer borders. He received 35 c.c. of Fuadin from May 20 to May 27, and a second course from June 3 to June 10. The lesions appeared healed after the second course, but he remained in the hospital because of the orthopedic problem. After about three weeks both scars ulcerated. Scrapings were negative for leishmaniasis. He was placed on systemic antibiotics and daily local therapy. On this program the lesions became progressively larger. Consequently, from July 15 to July 24 he received 50 c.c. of Fuadin, with complete healing. He suffered moderate arthralgia during the last three days of the second course and on the last day of the third.

Case 10. A 21 year old white male soldier was admitted on June 17, 1955.

On approximately May 10, 1955, he had noted the appearance of two papules on the dorsum of the right forearm and one on the right side of the neck which ulcerated in about one week. These lesions had gradually increased in size in spite of local therapy.

The patient had been in Camp Pina from January 20 to March 10, and in an adjacent camp from March 10 to June 10. He had been on night jungle maneuvers in late February and early March, and during the first week in April. He always wore gloves but no mosquito helmet. He slept on his left side with both hands under his head, and recalled many insect bites about the wrists, hands, neck and face.

Physical examination on admission revealed 0.5 cm. oval ulcers, two on the dorsum of the right forearm and one on the right side of the neck, with raised red borders and necrotic bases. He had a 3 cm. right axillary node.

Basic laboratory studies gave normal results.

The diagnosis was made on the basis of a positive scraping from the borders of two of the ulcers.

He received 35 c.c. of Fuadin from June 17 to June 24, and a second 35 c.c. from July 1 to July 7. He suffered from moderate arthralgia during the last two days of the first course and the last four days of the second course. Lesions appeared healed by July 10.

GENERAL CONSIDERATIONS

The histories and the findings in these cases were very carefully studied in an effort to establish how, when and where they had become infected.

This disease is generally believed to be transmitted by the bite of an infected sandfly. The area in which these soldiers were operating was heavily infested with the phlebotomus fly. All the patients recalled this

particular pestilence vividly. No history was given to suggest that any other insect might be incriminated. All had been exposed in relatively virgin forest areas. No statement can be definitely made about the means of infection, but there is every reason to suspect the sandfly, no reason to suspect another insect vector, and no grounds on which to acquit the sandfly.

All of the patients had been exposed in the Camp Pina area near the banks of the fabled Chagres River on the Atlantic side of the Isthmus of Panama, within the Panama Canal Zone. When the locations of the lesions were tabulated it was noted that eight of the 10 patients had lesions on the hands, wrists or forearms, and that all of the lesions were on areas exposed in a fully dressed state, taking into consideration the idiosyncrasies noted in the histories. Careful questioning revealed that while in the camp



Fig. 1. Case 4. This patient habitually sleeps on his back with both hands behind his head. The lesions therefore occupy perhaps the only exposed surface while he is sleeping fully dressed with gloves and head net.

itself the soldiers wore no gloves, nets or repellent, and frequently slept and went about openly in various stages of undress. There was nothing whatsoever to indicate that, in the camp area itself, the sites of the lesions had been selectively exposed, nor did any patient recall any appreciable trouble from insect bites. However, while on jungle maneuvers the patients remained dressed throughout and wore mosquito helmets and mosquito gloves, with the exceptions noted. A very careful investigation of each man's sleeping habits was made. First he was asked to describe the position he generally slept in, then he was asked to recheck his sleeping position, and finally each patient was carefully observed while sleeping on the ward. Thus the records in the case histories are felt to be quite reliable. A very striking correlation was found between the areas which would be exposed while sleeping in the normal manner and while clothed as described.

and the location of the lesions on the bodies (figure 1). As a result, it is felt that one can probably justifiably assume that all patients were infected while on jungle maneuvers, probably at night, while sleeping. The one patient with the lesion in the popliteal area in all probability became infected on that one particular night when he had occasion to remove his trousers. The patient with the midcalf lesions undoubtedly became infected because of his habit of rolling his trousers up above boottop level. In two patients (cases 3 and 10) a strong possibility exists that there was secondary spread from scratching.

As to the time of infection, once again no positive statements can be made. The dry season in this area extends from mid-December to the end of May. All patients were undoubtedly infected in this period, inasmuch as none (with the exception of case 8) had been in the area prior to the beginning of the dry season, and all lesions had appeared before the end of the dry season. If the conclusion that they were all infected on night jungle maneuvers is tenable, then they were all infected within the period of January 26 to April 20, and seven of the 10 were infected in late February and early March. It is felt that case 5 was infected on the night of March 3, and that the popliteal lesion incurred by case 6 was acquired on that same date.

INCUBATION PERIOD

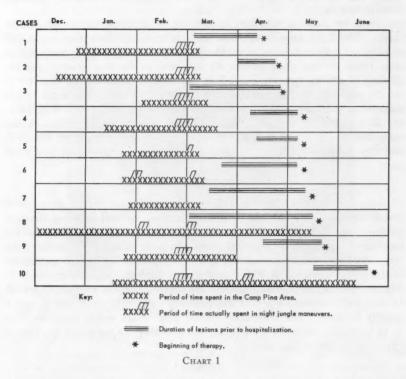
Rees and Hamlin ² have stated that the incubation period varies from twenty days to eight months. When the time interval between the first possible presumed exposure in our cases and the appearance of the lesions is considered, the incubation period could not have exceeded 11 weeks (case 10). In those cases who left the areas of exposure before the appearance of the lesions (cases 2, 4, 5, 6, 7 and 9), the periods ranged from about 14 days to 35 days, and should represent the shortest possible incubation period. In case 5 the incubation period was probably exactly 42 days, and in case 6 exactly 32 days. The incubation period in all cases would therefore have to lie within a two to 11 week span, and probably, as suggested in chart 1, varied from two to six weeks.

Course

There is another very obvious measurable time interval demonstrated by chart 1, the time from the first appearance of the lesions until they were given serious medical attention. This period was largely occupied by the time required to develop a skin lesion which was obviously something other than the perennial insect bites and superficial skin infections noted in all soldiers operating in the jungles. The dates of admission very nearly represent the dates on which the diagnoses were suspected. When these dates are considered, it is seen that this period measured from two to 10 weeks, and averaged nearly four weeks. Though this time interval is appreciable,

it is still less than that recorded in case reports in the literature of patients who escaped from the area of high clinical suspicion before the lesions appeared or were seriously studied.

These two time intervals—the incubation period and the time lapse after the appearance of the lesion until it received serious medical attention—when added together must be counted in months. This is quite important, inasmuch as any individual case can travel far in that time. For example, the case of Rees and Hamlin was incurred in Venezuela and diagnosed in



San Francisco; ² a case reported by Snapper was incurred in Colombia and diagnosed in New York.³ If patients with this lesion travel far enough or to the wrong places, one might need also to add a period of time represented by nondefinitive and ill-advised therapy. If the lapse of time becomes long enough, it may very well extend beyond the period of optimal diagnosability. Snapper has stated that smears, cultures and biopsies, the three primary diagnostic procedures, are very unsatisfactory after secondary bacterial invasion has become well established.³ The organisms are said to be very difficult to find in scrapings after five to six weeks.² In our cases

there was a pronounced negative correlation between the age of the lesion and the ease of finding the organism on scrapings.

These factors assume specific importance inasmuch as the area in which all these cases were incurred is used as a training area for units moved in for short periods from remote stations, and cases from this area may well show up far away.

DIAGNOSIS

The clinical features of a classic case—the oval, painless, indolent ulcer with the raised dull red border, the necrotic base and the beadlike subcutaneous nodules—are almost diagnostic (figure 2). It was very striking



Fig. 2. Case 5. In this case a black dot was painted on the skin over each palpable subcutaneous nodule as nearly as possible the same size as the nodules. This string of nodules extended from the ulcer to an enlarged axillary node.

how similar the lesions in all these cases were. However, a broad differential diagnosis, including chancre, beryllium granuloma, skin tuberculosis, cat scratch granuloma, sarcoid, Wegner's granuloma, ecthyma, glanders, sporotrichosis, blastomycosis and chronic nonspecific bacterial infections, must be considered. It should, moreover, be very strongly emphasized that a purely clinical diagnosis is not sufficient. During the period of time in which these cases were collected, approximately 10 cases of cutaneous ulcers which in appearance were strongly suspected of being the result of leishmania were also very thoroughly studied by repeated scrapings, all of which were negative. All of the lesions of these latter patients healed quite promptly with good local therapy. There were, however, no cases with the charac-

teristic beadlike nodules in which the organism was not found. As a result of this experience it is felt that an etiologic diagnosis is mandatory.

HISTOLOGIC DIAGNOSIS

To approach more rationally the matter of establishing an etiologic diagnosis, it is most helpful to be cognizant of the histopathology in this disease. This was described by Thornburgh, Johnson and Elton ⁴ as an intense chronic inflammation of the dermal papillae with pseudoepitheliomatous hyperplasia and underlying granulomatous inflammatory reaction. The dermal papillae tend to become necrotic and slough, leaving a small amount of poor quality granulation tissue at the base. The ulcer then expands by concentric zones of parasitic expansion just under the epidermis,

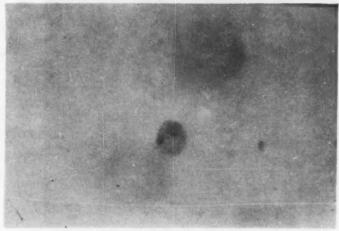


Fig. 3. The leishmania organism noted here demonstrates fairly well the characteristic histologic features. The larger fainter cells are red cells.

among the dermal papillae.⁴ The raised red border represents this expanding zone of active inflammation. As such, it is the locus of active disease and the place from which the best material for diagnostic purposes can be obtained.

The procedure used here was to apply cold saline compresses initially until the crusts and purulent material were cleaned up. Then the area was blocked with procaine, and the under surfaces of the raised borders were scraped with a small curette. The material obtained was then smeared on a slide like an ordinary blood smear and stained with Wright's stain. With this procedure 100% positive smears were obtained, whereas scrapings from the base of the ulcers were not positive in all instances attempted. This exact procedure was not utilized on the first three cases largely because of

inexperience and inadequate information, and resulted in a need to resort to biopsy for diagnosis.

On smears prepared in this manner the organism is very characteristic (figure 3). Its features are as follows:

- 1. Small in size, measuring 2 to 5 μ in the longest diameter. An appreciation of the size is vital, as they cannot be seen well except under oil immersion. Unless one is prepared to search carefully for something very small, they may be very easily overlooked.
- Oval in shape. The exact shape was noted to be somewhat variable, being more rounded in the newer lesions.
- 3. Well defined cell borders.
- 4. Light blue cytoplasm.
- 5. Large, relatively pale trophonucleus at one end of the cell.
- 6. Dark, rod-shaped blepharoblast. This may be seen in many positions within the cell and is its most striking feature.

These organisms may be seen either singly, in groups or within the structure of large macrophages. When seen on histologic section the organisms show the same features, except that in our specimens they were almost spherical.

The visualization of the organism is diagnostic. However, it is felt by some that the histopathology is so characteristic that it is diagnostic when studied by skilled pathologists.⁴ All of these cases were positively diagnosed: three by positive biopsies, two by positive smears and positive biopsies, and five by positive smears only. Attempts were made on four cases to culture the organism on a makeshift media, all of which were unsuccessful. It was impossible to do any work with the skin test of Montenegro because of the unavailability of the skin testing material.

TREATMENT

Every effort was made to determine whether this was a localized or a systemic disease. The fact that none of the patients acted, looked or felt ill, and that rather thorough studies showed no abnormalities, proved to be the best evidence against this being a systemic illness. Yet eight of the 10 cases showed abnormalities on physical examination beyond the confines of the ulcer itself, either in the form of the beadlike, nontender subcutaneous nodules or enlargement of the regional lymph nodes. It has been suggested that the lymphatic abnormalities are due to secondary infection. However, the lymphatic enlargements were uninflamed and nontender; the peculiar beadlike nodules, sometimes called plastic lymphangitis, have never been noted by the author in any other condition; and the lymphatic findings did not improve in the three cases that received courses of antibiotics prior to definitive therapy. Furthermore, it has been shown on histologic study that the small, beadlike nodules are heavily infested with the parasites, with

very little acute purulent inflammatory reaction. These nodules are believed to represent an inflammatory reaction due strictly to the presence of the parasite.^{4, 1} It was felt that the disease as seen, was not systemic in the general sense of the word, but that it was not localized to the actual site of ulceration. In support of this contention, subcutaneous nodules removed surgically in two cases were both found to be heavily infested with parasites. No biopsies were made of actual enlarged lymph nodes.

If, then, this is not a simple ulcer, such forms of therapy as dry ice, x-ray therapy, local injections of tartar emetic or atabrine and simple excision are not adequate. On the basis of such reasoning, the decision was made to utilize a systemic medication in the form of Fuadin. There is no uniform opinion as to how this medication should be administered. The first 10 patients treated were given Fuadin in courses of 5 c.c. per day intramuscularly for seven days, then a week of rest, followed by a repeat course, until the lesions were healed.

HEALING TIME

The case treated by Rees healed in about three months.² In general, it is reported that healing requires from five to seven weeks.⁵ The healing times in our cases, with the duration of follow-up, were as follows:

	Healing Time	Follow-Up
1.	27 days 25 days	Recurrence in 5 weeks 1 Month
2.	28 days	51 Months
3.	25 days	51 Months
4.	26 days 23 days	Recurrence in 5 weeks 31 Months
5.	25 days	51 Months
6.	25 days	51 Months
7.	16 days	51 Months
8.	15 days 10 days	Recurrent after 7 weeks 2 Months
9.	24 days 16 days	Recurred in 3 weeks 4 Months
10.	24 days	4½ Months

Of the 10 cases treated on this program, there were four recurrences. Though the organism could be found only with great difficulty, it was nonetheless felt that they were genuine recurrences because of the failure to respond to antibiotic and local therapy and the prompt response to Fuadin. Furthermore, the fact that the recurrent ulcers were often doughnut-shaped, with intact skin in the center, is in keeping with the established histopath-

ology of this disease. The recurrences became apparent in from two to seven weeks. Since all other cases have been followed for at least four and one-half months, it is felt that this probably represents the true incidence. The apparent healing time varied from 15 to 28 days, with six of the cases requiring approximately four weeks or less. It is felt that the time required for healing cannot be well evaluated because of the high incidence of recurrences. It was quite difficult to determine just when an ulcer was healed; in fact, the most consistent criticism of the program by local observers was that entirely too much treatment was being given. The results did not support this latter opinion, and it is felt that the four temporary failures may be attributed solely to inadequate therapy, since they promptly responded to more Fuadin. Surely one may conclude that the disease is treatable with Fuadin, since there were no ultimate failures.

SAFETY

The antimony drugs, including Fuadin, have well established toxicity. Experimental work has shown a definite toxicity to the kidney, liver, myocardium and gastrointestinal tract. Mainzer and Krause reported sinus bradycardia and T wave changes in the electrocardiogram after tartar emetic. Tarr reported 100% T wave changes after tartar emetic and 53% after Fuadin. In the treatment of schistosomiasis with 100 c.c. courses of Fuadin, Most et al. found the following:

- 1. Electrocardiographic changes as follows:
 - 11% showed increased amplitude of P waves in II and III.
 - 45% showed fusion of the ST segment and T waves.
 - 99% showed decreased amplitude of T waves.
 - 27% showed an increased QT interval.
- 2. One case in 400 developed toxic hepatitis.
- 3. General symptoms as follows:
 - 66% had nausea.
 - 52% had vomiting.
 - 52% had arthralgia.
 - 7% had conjunctivitis.
- 4. There were no reported cases of renal changes.9

Cleve reported two cases of acute toxic myocarditis due to tartar emetic.¹⁰ Kazzaz and Tabhara, on the other hand, noted no electrocardiographic changes in experimental work with dogs.¹¹

The purpose of the study of these cases was not necessarily to establish the existence of toxicity to antimony, but rather to measure its extent in patients of this type, with this disease, on this particular therapeutic regimen. To measure this each patient, in addition to the basic laboratory studies mentioned, had (1) a 12-lead electrocardiogram prior to therapy, at the conclusion of each course of therapy, and one and three weeks after com-

pletion of therapy; (2) 45 minute Bromsulphalein retention studies prior to therapy, at the end of each course, and until they returned to normal; (3) urinalysis three times weekly; (4) daily clinical evaluation.

In an evaluation of the electrocardiograms (table 1), nine out of the 10 patients showed diminution of the amplitude of the T waves after the first

TABLE 1

Cases	T Wave Changes in the 1st Course	Changes in 1st and 2nd Courses	Merging of ST and T Waves	P Wave Changes
10	9	10	6	4

35 c.c. of Fuadin, and the tenth patient showed the changes after the second 35 c.c. In all cases the findings were more marked with increasing treatment. Six of the 10 patients showed a fusing of the ST segments and T waves, as noted mainly in the chest leads. Four of the 10 patients showed an increase in the amplitude of the P waves in either Lead II or Lead III, or both. In only two cases were the electrocardiographic changes of a degree to classify the tracing as an abnormal record. No consistent changes were noted in the cardiac rates or the QT intervals.

Of the tracings taken after therapy, all 10 showed improvement after a one-week interval, and the seven cases in which a three-week tracing was taken all had reverted to normal (figure 4).

The results of the studies of hepatic toxicity as measured by 45 minute Bromsulphalein retention were as follows:

TABLE 2
Per Cent of Bromsulphalein Retention

Case	Prior to Rx	After 1st Course	After 2nd Course	After 3rd Course	1 Wk. after Completion
No. 1	2%	2%	2%	3%	
No. 2 No. 3	2%	2%	3%		
No. 4 No. 5	3%	5%	20%	4%	8%
No. 6 No. 7	3%	14%	6%		2%
No. 8 No. 9	2%	2%	4%	4%	. 1
No. 10	4%	6%	12%	- 70	8%

As noted, all of the 10 patients showed a numerical increase in the Bromsulphalein retention which, in most cases, was very slight and probably insignificant. However, four patients developed an abnormal level of Bromsulphalein retention which apparently was reversible, as measured by tests done one week later. In no case were there any notable symptoms, liver swelling or liver tenderness.

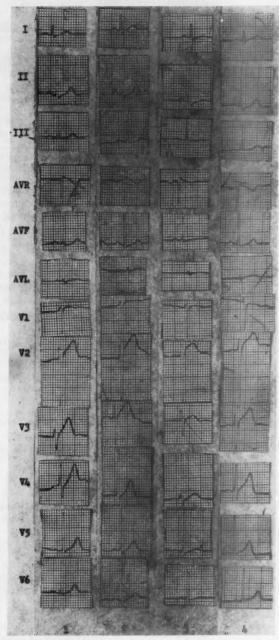


Fig. 4. Typical electrocardiographic changes as recorded in case 3. (1) Prior to treatment. (2) At the completion of the first course. (3) At the completion of the second course. (4) One week after completion of therapy.

In no urinalysis performed on any of the patients were abnormalities noted.

In the daily evaluation of the patients no complaints were elicited except for aching of the joints. At no time were any joint abnormalities noted. The incidence of arthralgia is shown below.

TABLE 3

Total Patients Taking	Arthralgia During	Patients Taking	Arthralgia During
1st Course	1st Course	2nd Course	2nd Course
10	4	8	8

The four patients who noted joint pains during the first course had only mild symptoms. However, symptoms during the second course were occasionally quite severe, requiring salicylates for relief. In all cases the arthralgia disappeared within 48 hours after treatment was completed.

No patient complained of nausea and vomiting, though two complained of anorexia.

Though the incidence of arthralgia and electrocardiographic abnormalities was very high and the incidence of liver toxicity was appreciable, they were all proved to be transient and of a low degree and, as such, were not felt to contraindicate the utilization of this program of treatment for this disease in otherwise healthy patients.

SUMMARY

- 1. Ten cases have been presented of proved cutaneous leishmaniasis in young white soldiers, contracted in the Camp Pina area of the Panama Canal Zone.
- 2. The conditions of infection, the incubation period and the course of the disease as observed in these cases have been discussed.
- 3. The diagnostic clinical and laboratory features of this illness have been described.
- 4. The results of treatment with Fuadin, including the occurrence of antimony toxicity, have been reported.
- 5. It is concluded that Fuadin is an effective and relatively safe form of treatment in otherwise healthy young white males with this illness, though the course of therapy is quite prolonged.

SUMMARIO IN INTERLINGUA

Durante le periodo ab april a junio 1955, 10 casos de leishmaniasis cutanee in juvene soldatos american blanc esseva admittite al Hospital Coco Solo a Cristobal, Zona del Canal.

Un meticulose analyse del historia e del constatationes physic in le 10 casos revelava que omne iste patientes habeva essite inficite in le region del bucca del riviera Chagres, probabilemente via morsuras de inficite musca de arena, sin dubita

durante que illes dormiva de nocte in le jungla. Le periodos de incubation (secundo nostre suppositiones) esseva inter duo e 11 septimanas e probabilissimemente inter duo e sex septimanas. Habeva occurrite un intervallo de duo a 10 septimanas ante que le lesiones esseva satis grande pro demandar serie attention medical.

Omne caso exhibiva characteristic ulceres oval indolente con bases necrotic e elevate margines de color rubie obtuse. Cinque casos exhibiva subcutanee tumescentias in forma de perla que non esseva sensibile sub pression. Omne le casos esseva diagnosticate per biopsia o frottis de grattage ab le dorso del elevate margines, que representa le loco active del morbo.

Omne le casos esseva tractate con Fuadina intramuscular, in cursos de un septimana de 5 cm³ per die, con intervallos de un septimana inter un curso e le proxime. Le apparente tempore de sanation variava inter 15 e 28 dies, sed in quatro casos il habeva recurrentias de maniera que le ver tempore de sanation non esseva computabile. Omne le patientes exhibiva provas electrocardiographic de toxicitate antimonial. Quatro patientes disveloppava anormal retention de Bromsulphaleina. Nulle del patientes monstrava anormalitates in urinalyses serial. Quatro del patientes habeva arthralgia durante le prime curso. Omne le patientes qui requireva un secunde curso disveloppava moderate grados de arthralgia. Omne le alterationes toxic esseva reversibile.

Nos opina que Fuadina representa un forma efficace de therapia, e ben que il habeva indicationes de un alte incidentia de toxicitate, le grados de severitate del toxicitate non esseva satis alte pro arguer contra le uso del droga in patientes de alteremente bon stato de sanitate.

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ANALGESIC PROPERTIES OF MIXTURES OF CHLORPROMAZINE WITH MORPHINE AND MEPERIDINE *

By George L. Jackson, M.D., and David A. Smith, M.D., Harrisburg, Pennsylvania

CLINICAL observations of the enhanced effectiveness of narcotics given with chlorpromazine have been reported by several investigators. 1, 2, 8, 4, 5, 6 These reports suggest that one may anticipate more complete and longer lasting relief from pain as a result of concomitant administration of these agents. Because of its potential value in reducing the amount of analgesic required, it seemed advisable to subject this observation to controlled clinical testing.

Accordingly, the following experiments were designed to determine:

- 1. Whether the method of testing would yield results comparable to those reported by Beecher and his associates relative to the analgesic properties of morphine.7, 8, 9
- 2. The analgesic properties of chlorpromazine administered alone.
- 3. The effects of combinations of chlorpromazine and morphine, and chlorpromazine and meperidine, in postoperative pain, with special emphasis on the smallest amount of narcotic which, when combined with chlorpromazine, would produce satisfactory analgesia.

To determine the magnitude of the problem and to choose a base line for this study, the records of the Harrisburg Polyclinic Hospital were reviewed. Fifty patient charts were randomly selected for every month in 1954, and the narcotics administered to each patient were recorded. Of these 600 records, 117 were on patients less than 18 years of age. Of the remaining 483 records, arbitrarily designated as adult group, 313 (65%) were on patients who received morphine, meperidine or codeine during hospitalization. Table 1 summarizes sex and age incidence and the average dose of each of the narcotics used.

EXPERIMENTAL PROCEDURE

All patients studied were either private or ward patients on the surgical service at the Harrisburg Polyclinic Hospital. The patients ranged in age from 18 to 72 years. Their weights ranged from 98 to 239 pounds. A total of 211 patients was studied. There were 150 females (71%) and 61

^{*} Presented at the Thirty-seventh Annual Session of The American College of Physicians, Los Angeles, California, April 20, 1956.

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males (29%). This unequal distribution is not felt to detract from the significance of the following observations.

Many patients were eliminated from the study because they required too few injections for pain relief. Only those patients who required three injections in 24 hours were included.

Nurse observers were used for questioning of patients. They were instructed not to introduce bias into their questioning, and efforts were made to avoid suggesting the performance of a clinical study.

The nurse observers obtained permission from the operating surgeon to include each patient in the study program preceding surgery, then confirmed the decision after surgery. The patient was interrogated concerning previous experience with analyseic drugs and abnormal responses to medication. The most frequent operative procedures were abdominal and orthopedic, although a small number of thoracic surgery patients are also included.

Table 1

Number of Patients and Average Dose of Analgesic

	No. of Patients	Mo	rphine	Co	deine	Мер	eridine
Groupings	on Analgesic	No. of Doses	Average Dose, mg.*	No. of Doses	Average Dose, mg.*	No. of Doses	Average Dose, mg.
Male	71	51	12.0	10	35.1	41	82.9
18-64 years	17	11	10.8	18	32.4	12	72.9
Over 64 years Female	11	11	10.0	,	34.4	12	12.7
18-64 years	200	91	12.5	91	31.8	148	73.1
Over 64 years	25	14	12.0	6	32.4	21	73.8
Total	313	167	12.2	122	32.7	222	75.6

^{*} Conversions were made for morphine and codeine from grains to milligrams where 1 gr. equaled 64.8 mg.

The patients were observed hourly for a minimum period of 16 hours after their return from recovery room. These hourly observations by the nurses included the vital signs and the amount, character and location of pain. A reproduction of the questionnaire is included (figure 1). The nurse was asked to classify the pain according to three grades: none (0), mild (1+), and severe (2+).

Whenever the patient complained of severe wound pain (constant aching at the site of incision), in contradistinction to intermittent pain, or pain from organ distention, the nurse was instructed to give the patient a test drug. Each drug was administered whenever the patient complained of severe pain, but never more frequently than once an hour. On subsequent patient visits, the nurse attempted to ascertain if the patient had pain relief and, if so, whether the relief was greater or less than 50%. To be considered as providing pain relief, a drug had to provide more than 50% pain relief

MALGESIC STUDY

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TABLE 2
Analgesic Responses to Morphine

Dose of Morphine (mg.) per 70 kg.	No. of Doses	Per Cent Relieved	Aver. Time Relieved, Hrs
Placebo	17	29	1.35
5	18	67	3.89
10	18	100	4.89
15	17	94	5.63

for a period of not less than two hours. The number of patients who obtained this response is expressed as "per cent relieved" in this paper.

All drugs supplied for testing purposes were coded. The four ampules to be given to a patient were packaged separately and coded so that without a protocol the contents of individual ampules were unknown. Thus, the nurse observers at no time knew the nature of the agents administered.

It should be noted that all experiments were designed by statisticians familiar with the problems of biologic testing.

RESULTS

A. Confirmation of Method: To train the nurse observers and to compare the technics with those discussed by Beecher, a group of 24 patients received at least two of the following drugs: placebo; morphine sulfate, 5 mg./70 kg. body weight; morphine sulfate, 10 mg./70 kg. body weight; and morphine sulfate, 15 mg./70 kg. body weight. These drugs were all given on the day following surgery.

Table 2 indicates the results. These figures are similar to those reported by Beecher and his associates 7, 8, 9, 10 (table 3). Because of this confirmation, we felt that the test procedures were reliable.

For the subsequent group of experiments, certain changes were made in the basic design and execution. These changes involved discontinuing the calculation of the dose of drug on the basis of body weight. In addition, it was decided to study patients immediately following their return from the recovery room. This seemed advisable for the following reasons:

Table 3

Analgesic Properties of Morphine (Beecher and Associates)

Dose of Morphine (mg.) per 70 kg.	% Relief	Duration of Relief in Hours	Reference
4-6	82.4	_	7
7-9	93.3	4.15	7
8	56.5 to 100	_	9
10	64.1 to 94.4	4.5±0.05	8
10	50.6 to 74.5	6.1 to 7.75	10
10-12	93.7	4.15	7
13-15	90.5	4.15	7

1. Clinical experience dictates alterations of narcotic doses based upon considerations of age and weight. These differences are measured in terms of several milligrams, and rarely in terms of 1 mg. or less. When exceedingly small doses of narcotics (i.e., 2.5 mg. morphine sulfate) were tested, deviations of a fraction of a milligram seemed insignificant or unimportant. Also, there was less chance for errors in measurement.

2. The pain experienced by patients immediately following an operation should be more amenable to the measurement of analgesic action.

To ascertain that a standard dose (not based on weight) for all patients would not alter the results, the data were first analyzed according to weight groups (tables 4 and 5).

Table 4
Per Cent Relief According to Weight Groups

Drug and Dosage		Weight Group	
Drug and Dosage	Less than 130 lbs.	130 to 170 lbs.	More than 170 lbs
Chlorpromazine, 20 mg. Morphine, 2.5 mg. Morphine, 5.0 mg.	64 (11) 64 (11) 60 (10)	79 (14) 45 (20) 86 (7)	33 (6) 60 (10) 73 (11)

Note: Numbers in parentheses indicate number of patients.

Table 5

Average Length of Relief in Hours According to Weight Groups

Davis and Davis		Weight Group	
Drug and Dosage	Less than 130 lbs.	130 to 170 lbs.	More than 170 lbs
Chlorpromazine, 20 mg. Morphine, 2.5 mg. Morphine, 5.0 mg.	2.00 (11) 2.91 (11) 2.60 (10)	2.43 (14) 1.70 (20) 3.71 (7)	1.17 (6) 2.00 (10) 2.82 (11)

Note: Numbers in parentheses indicate number of patients.

One would anticipate that if weight were critical, the percentage relief would be highest for the smallest weight and decrease as weight increased. However, this does not appear to be the case for the doses studied.

B. Chlorpromasine: Chlorpromazine was given to various groups of patients in doses of 5 mg., 10 mg. and 20 mg.* After preliminary testing it seemed that no useful purpose would be served by studying extensively the 5 mg. dose level. Accordingly, efforts were concentrated upon defining the analgesic properties of 10 mg. and 20 mg. of chlorpromazine.

Twenty-six patients received 10 mg. doses of chlorpromazine, with relief of pain in 54% for an average of 2.08 hours. Thirty patients received

*Chlorpromazine (Thorazine) for this study was supplied by Smith, Kline & French Laboratories, Philadelphia, Pennsylvania.

CHLORPROMAZINE RESPONSE

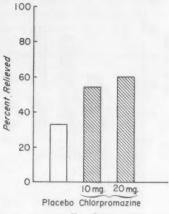
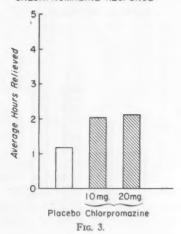


Fig. 2.

20 mg. of chlorpromazine, with relief of pain in 60% for an average of 2.26 hours. The 122 doses of placebo given were found to have an average effectiveness of 33% for an average of 1.38 hours. All these results are illustrated in figures 2 and 3. It seems apparent that chlorpromazine alone is capable of producing pain relief. Furthermore, there is no statistical difference between the two doses studied.

C. Morphine: Morphine, 2.5 mg., administered to each of 44 patients, provided pain relief in 48% for an average of 1.93 hours. Similarly, 5 mg.

CHLORPROMAZINE RESPONSE



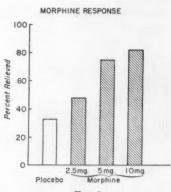


Fig. 4.

of morphine, administered to 28 patients, gave pain relief to 75% for an average of 3.22 hours, whereas 10 mg. of morphine produced pain relief in 82% of 11 patients for an average of 2.90 hours. The results are illustrated in figures 4 and 5.

D. Chlorpromazine-Morphine Combinations: The combination of 2.5 mg. morphine and 5 mg. chlorpromazine in 16 subjects relieved pain in 81% for an average of 3.00 hours. The combination of 2.5 mg. morphine sulfate and 10 mg. chlorpromazine in 12 subjects relieved pain in 75% for an average of 2.36 hours. The combination of 2.5 mg. morphine sulfate and 20 mg. chlorpromazine in 51 subjects relieved pain in 73% for an average of 3.70 hours. Finally, the combination of 5 mg. morphine sulfate and 10 mg. chlorpromazine in 11 subjects relieved pain in 73% for an average



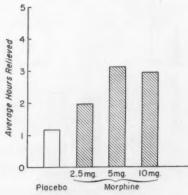
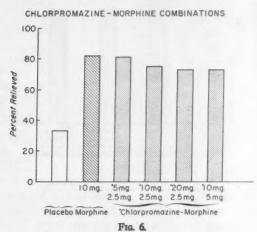
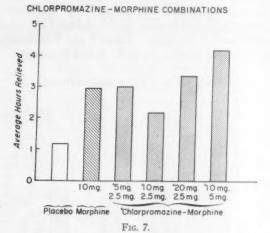


Fig. 5.

of 4.38 hours. These responses are compared with responses to 10 mg. of morphine alone in figures 6 and 7.

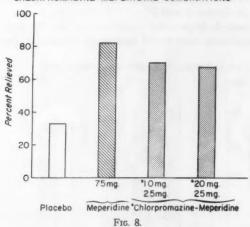
E. Chlorpromazine-Meperidine Combination: In the same patients, 75 mg. doses of meperidine were tested against 25 mg. meperidine plus 10 mg.





chlorpromazine, and against 25 mg. meperidine plus 20 mg. chlorpromazine. The results are illustrated in figures 8 and 9. These figures indicate that chlorpromazine when combined with meperidine increases meperidine's analgesic effectiveness, so that 25 mg. of meperidine plus 10 mg. or 20 mg. chlorpromazine are capable of relieving postoperative pain in a manner

CHLORPROMAZINE-MEPERIDINE COMBINATIONS



comparable to 75 mg. of meperidine. These figures for meperidine alone are somewhat different from those reported by Lasagna, who found 100 mg. meperidine effective in 61.9% of his patients for 6.78 hours.

F. The Effect of Previously Administered Chlorpromazine: When the work sheets for statistical analysis were reviewed it was observed that the previous administration of chlorpromazine influenced the effectiveness of subsequently administered morphine. Tables 6 and 7 demonstrate this and summarize the data from Sections B, C, D, E and F above.

CHLORPROMAZINE-MEPERIDINE COMBINATIONS

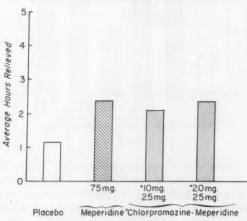


Fig. 9.

TABLE 6 Analgesic Properties of Various Drugs

		Per Cent Relief	
Drug Tested	Doses Not Preceded by Chlorpromazine	Doses Preceded by Chlorpromazine	Over All Average
Placebo	27 (81)	44 (41)	33
Chlorpromazine 10 mg.	50 (18)	63 (8)	54
Chlorpromazine 20 mg.	70 (23)	29 (7)	60
Morphine 2.5 mg.	37 (30)	71 (14)	48 75 82
Morphine 5.0 mg.	60 (15)	92 (13)	75
Morphine 10.0 mg.	50 (4)	100 (7)	82
Morphine 2.5 mg. plus			
chlorpromazine 5 mg.	100 (7)	67 (9)	81
chlorpromazine 10 mg.	50 (6)	100 (6)	75
chlorpromazine 20 mg.	68 (40)	91 (11)	73
Morphine 5.0 mg. plus	1		
chlorpromazine 10 mg.	100* (7)	25 (4)	73
Meperidine 75 mg.	83 (12)	81 (16)	82
Meperidine 25 mg. plus			
chlorpromazine 10 mg.	68 (19)	75 (8)	70
chlorpromazine 20 mg.	59 (22)	100 (5)	67

() Indicates the number of patients observed. * Statistically significant @ P=.05.

Because of the small sampling of patients, many of these figures fail in application of the usual statistical yardstick. Nevertheless, they offer an indication of the results to be anticipated. Precedent for this comment is to be found in Lasagna's recent article 16 and Starr's editorial. 16

TABLE 7 Analgesic Properties of Various Drugs

a divo	A	verage Hours of Rel	lief
Drug Tested	Doses Not Preceded by Chlorpromazine	Doses Preceded by Chlorpromazine	Over-All Average
Placebo	1.20 (81)	1.76 (41)	1.38
Chlorpromazine 10 mg.	1.94 (18)	2.38 (8)	2.08
Chlorpromazine 20 mg.	2.32 (23)	1.20 (7)	2.26
Morphine 2.5 mg.	1.46 (30)	2.92* (14)	1.93
Morphine 5.0 mg.	2.27 (15)	4.42 (13)	3.22
Morphine 10.0 mg.	2.50 (4)	3.17 (7)	2.90
Morphine 2.5 mg. plus			
chlorpromazine 5 mg.	4.00 (7)	2.13 (9)	3.00
chlorpromazine 10 mg.	1.17 (6)	3.80* (6)	2.36
chlorpromazine 20 mg.	3.63 (40)	4.00 (11)	3.70
Morphine 5.0 mg. plus			
chlorpromazine 10 mg.	6.00* (7)	1.67 (4)	4.38
Meperidine 75 mg.	2.70 (12)	2.80 (16)	2.76
Meperidine 25 mg. plus			
chlorpromazine 10 mg.	1.81 (19)	3.17 (8)	2.18
chlorpromazine 20 mg.	2.52 (22)	3.40 (5)	2.69

() Indicates the number of patients observed. * Statistically significant @ P=.05.

COMMENTS

These results indicate that the addition of chlorpromazine to morphine sulfate and meperidine hydrochloride is capable of increasing the analgesic properties of minimally effective doses of these narcotics. Previous administration of chlorpromazine also accentuates the analgesic activity of morphine sulfate. It should be noted that the graphs shown above compare the average responses. Similar graphs showing the analgesic activity of only those doses not preceded by chlorpromazine would be even more impressive.

Vital signs recorded on the patients studied in this group of experiments have demonstrated no tendency to depression of respiratory rate or blood pressure. However, this is not a critical method of settling this issue. It is to be hoped that, by utilizing such small doses of narcotics for the relief of pain, the associated depression of cough reflex and respiration may not be observed.

Lee ¹¹ has shown that doses of 9.6 to 13.1 mg. of morphine in 799 cases resulted in a slight decrease of respiratory rate (0.6 to 0.9 per minute). Keats's ⁸ figures are very much the same. This suggests that smaller doses would cause even less change. Dobkin ¹² reports depression of tidal volume with increase in respiratory rate after administration of chlorpromazine. With higher doses (1 to 2 mg./kg.), patients complained of conscious respiratory effort. Reckless ¹⁸ has demonstrated that chlorpromazine reverses morphine-induced respiratory arrest.

During the progress of this study, certain observations referable to the design of experiments for clinical testing were made. At one phase, the experimental design included the use of only a placebo and chlorpromazine. Approximately 60% of patients receiving a placebo were relieved of pain, and approximately 80% of patients receiving 20 mg. chlorpromazine were relieved. These results were not comparable to previous experience and were attributed to the inability of the patients and/or the nurses to distinguish significant pain relief in the absence of an active standard. Accordingly, the experiment was redesigned to include a morphine standard. and the results were considerably different. Another observation of importance in designing this type of experiment related to the effectiveness of an agent depending upon the amount of time elapsed between operation and administration of test drugs. It has been stated by Keats 9 that there is no greater tendency for the later doses of a drug to be more effective than the first dose of the same drug. We could not substantiate this. two observations will be the subject of separate papers.

The method of action of combinations of chlorpromazine with a narcotic is not known. It has been demonstrated that when solutions of morphine and chlorpromazine are combined, the identity of each remains the same and no third chemical structures are formed.¹⁴ It may be an expression of

altering pain stimuli at two levels in the central nervous system. Courvoisier 1 has reported that chlorpromazine makes the nerve cell more sensitive to action of narcotics and decreases the respiration of the cerebral cortex.

SUMMARY

1. The analgesic property of chlorpromazine in the relief of postoperative pain has been evaluated.

2. When chlorpromazine is combined with morphine, the analgesic properties of the combination are greater than those of either drug alone.

3. The addition of chlorpromazine to 25 mg. of meperidine hydrochloride produces an analgesic response similar to that seen with 75 mg. of meperidine hydrochloride.

4. Chlorpromazine administered prior to morphine increases the analgesic effectiveness of the second agent. Likewise, chlorpromazine administered prior to certain combinations of morphine and chlorpromazine appears to increase the effectiveness of the combinations.

ACKNOWLEDGMENTS

The authors express their sincere appreciation to Dr. R. E. Barto, Jr., Dr. L. G. Crawford, Dr. E. F. Fackler, Dr. T. J. Fritchey, Dr. G. L. Gleeson, Dr. R. L. Harding, Dr. S. C. Klemek, Dr. J. Lynch, Dr. W. K. McBride, Dr. D. E. Morrison, Dr. T. Outland, Dr. C. C. Pool, Dr. M. A. Silver and Dr. R. E. Stoner, Jr.; to Miss A. Janoscrat, Miss S. Nauss, Miss E. Nichols and Miss J. Reichenbach; to the personnel of the Nursing Office, Harrisburg Polyclinic Hospital; to Mr. J. L. MacFarland, administrator of Harrisburg Polyclinic Hospital, and to Mrs. E. D. Carlson, for their cooperation during the progress of this study.

SUMMARIO IN INTERLINGUA

Observationes clinic del meliorate efficacia de narcoticos administrate in association con chlorpromazina ha essite reportate per plure investigatores. Iste observation ha essite testate in un studio a controlo clinic "duple-secrete."

Le proprietates analgesic de varie doses de sulfato de morphina, hydrochlorido de meperidina, chlorpromazina, e mixturas continente chlorpromazina con morphina o meperidina esseva observate in 211 patientes post-operatori.

Le resultatos indica que chlorpromazina sol es un analgesico dulce. In un dose de 10 a 20 mg, alleviamento de dolor esseva observate in 54 a 60% del patientes con durationes de 2,08 a 2,26 horas.

Sulfato de morphina in un dose de 2,5 g produce alleviamento de dolor in 46% del patientes pro un duration de 1,77 horas. Le addition de 10 a 20 mg de chlorpromazina a 2,5 mg de sulfato de morphina produce alleviamento de dolor in 73 a 75% pro 2,36 a 3,7 horas. Isto debe esser comparate con sulfato de morphina in un dose de 10 mg que produce alleviamento de dolor in 82% pro 2,9 horas. Es demonstrate que previe administrationes de chlorpromazina augmenta le proprietate analgesic de subsequentemente administrate morphina e certe combinationes de morphina con chlorpromazina.

Chlorpromazina in doses de 10 o 20 mg in combination con meperidina in doses de 25 mg produce alleviamento de dolor comparabile al effecto de meperidina in doses de 75 mg.

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AN ANALYSIS OF 200 ADMISSIONS FOR MASSIVE UPPER GASTROINTESTINAL BLEEDING *

By S. L. ZIMMERMAN, M.D., F.A.C.P., EDWARD F. ENGEL, M.D., BERNARD LAPIDUS, M.D., EDWARD A. BRADLEY, M.D., and HUBERT CLAYTOR, M.D., Columbia, South Carolina

It appeared of great interest to the medical staff at this hospital to analyze critically the results of treatment of upper gastrointestinal bleeding. Accordingly, all such admissions between 1947 and June, 1953, were reviewed and subjected to critical analysis. It was at once apparent that certain arbitrary standards would be necessary for such analysis, and it was accordingly decided to include all admissions with upper gastrointestinal bleeding whose red blood count was less than 3.5 million, or whose hemoglobin was less than 10 gm. at the onset of therapy, or at any time subsequent to the initiation of therapy. Because we did not strictly adhere to the admission hemogram alone, those patients who had a significant hematocrit drop following rehydration were not lost to the study. The main objective was to ascertain the mortality due to bleeding per se, and to compare our results with those generally reported in the literature. A significant aspect with respect to this study was the critical reassessment of the adequacy of the regimen in effect, both medical and surgical.

Peptic ulceration is the most common cause of upper gastrointestinal hemorrhage; hence, as in other series, this source of bleeding constituted 61.5% of our admissions for upper gastrointestinal bleeding. Ivy, Grossman and Bachrach, in their extensive review, concluded that 72% of upper gastrointestinal bleeding was due to peptic ulcer. Approximately 25% of peptic ulcer patients bleed at one time or another, and, similarly, approximately one ulcer case in four is admitted to the hospital for bleeding. cite an over-all mortality of 7.5% due to bleeding, and hence approximately 1.6% of patients with peptic ulcer die from hemorrhage. The severity of bleeding varies considerably from case to case. Allen and Benedict,2 in an analysis of 628 cases of peptic ulcer with hemorrhage, classified 40% as mild, 28% as moderate and 32% as severe. In Baker's analysis of 497 cases, 43% were classified as mild (hemoglobin above 60%), and 18% as severe (hemoglobin below 30%).

^{*} Received for publication April 2, 1956. From the Medical Service, Veterans Administration Hospital, Columbia, South Carolina, Dr. S. L. Zimmerman, Chief.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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The age of the patient is of great importance with respect to mortality—the older the patient the higher the mortality in any large series. The average mortality, correlated with age, as obtained from the literature, may be roughly stated as follows:

Below 40	4%
Above 40	12%
Below 50	5%
Above 50	15%
70-79	25%
80-	50%

Severity of bleeding as correlated with mortality has been reported by Sullens et al. ⁴ In an analysis of 121 cases with less than 3,000,000 red blood cells, there were 19 deaths, a 16% mortality. However, of 99 cases with a red blood count greater than 3,000,000, there were only five deaths, a mortality of 5%. Recurrent hemorrhages or relapses while a patient is undergoing treatment in a hospital are of serious consequence. Babey and Hurst ⁵ reported a 27% mortality; Holman, ⁶ a 46% mortality; Baker, ⁸ a 31% mortality, and Nevin, ⁷ a 53% mortality in cases who had relapsed.

Without relapse, none showed a mortality greater than 10%.

Bleeding from gastric ulcers is about twice as hazardous as from duodenal ulcers. Ivy et al., in a review of 1,080 cases of gastric ulcer with hemorrhage, reported a mortality of 16.7%, and of 2,150 cases of duodenal ulcer handled similarly, an 8.8% mortality. In 1938 Miller and Elsom,8 reporting on 5,843 cases from the literature, treated mostly with a starvation regimen, showed a mortality rate of 8.7% (9.1% if prompt feeding cases were omitted). Meulengracht 9 made the observation that frequently patients with protracted hemorrhage stopped bleeding when fed, and that ambulant patients often recovered from severe melena without making any particular changes in their diet. Following this he began treating his patients with a bland diet of five meals a day. In 1947 he reported the results of 1,031 consecutive cases of bleeding peptic ulcer so treated. The gross mortality rate was 2.5%, but when those who died within 24 hours were excluded the net mortality was 1.5%. Rasberry and Miller 10 in 1943 reported on 2,111 collected cases of prompt feeding, with a gross mortality rate of 4%; when those moribund on admission or dying from other causes were excluded the net mortality was 1.9%.

The lowest recorded mortality for routine surgical therapy of chronic peptic ulcer during severe hemorrhage is that of Finsterer, 11 who reported a rate of 5.1% in 78 cases operated on within 48 hours after the onset of hemorrhage. Miller and Elsom 8 found an average mortality rate of 28% in 380 cases treated by surgery. However, one must bear in mind the fact that surgery is generally reserved for the cases with more severe or recurrent bleeding. Accordingly, it would not be reasonable to compare surgical versus medical statistics per se without considering these factors. Most surgeons have felt that their high mortality rate is the result of excessive

delay in surgical intervention in patients who continued to bleed or who had had recurrent hemorrhages. Ivy et al., in reviewing 155 cases with early operations, had a mortality rate of only 1.8%. With delay (over 48 to 72

hours), 39.7% died.

Cirrhosis of the liver is complicated by upper gastrointestinal bleeding in about 30% of cases. Douglass and Snell ¹² reported on 444 cases, and Fagin and Thompson ¹⁸ reported on 71 cases of cirrhosis, with 39.9% having massive hemorrhage. Palmer, ¹⁴ in a review of 994 patients with massive hemorrhage, found that 12.6% had demonstrable esophageal varices. Higgins ¹⁵ in 1947 reported on 115 patients with varices, of whom 50% died from hemorrhage. Weinberg ¹⁶ reported on 210 patients with esophageal varices, of whom 53.5% hemorrhaged.

Our series of 200 admissions is broken down as follows:

	Total Admissions	Total Deaths	Deaths Due to Bleeding
I Duodenal ulcer with bleeding	123 61.5%	3 2.4%	.813%
II* Prolapse with bleeding	10 5%	0	0
II Bleeding, site undetermined	13 6.5%	7.8%	0
IV Gastric ulcer with bleeding	22 11%	5 22%	3 13.6%
V Cirrhosis with bleeding	29 14.5%	8 (coma in 7) 27.6%	3.4%
VI Gastric malignancy with bleeding	3 1.5%	3 100%	3 100%
Total admissions for bleeding Mortality per cent	200	20 10%	8

^{*} One patient admitted five times.

Duodenal Ulcers: With respect to the duodenal ulcer patients, there were three deaths in this group, but bleeding per se was the actual cause of death in only one. This Negro patient was admitted with symptoms of perforation and abscess. His subphrenic abscess was drained and he bled postoperatively. Despite frequent daily transfusions he had a massive recurrence of bleeding and died. Autopsy revealed duodenal ulcer eroding the pancreatico-duodenal artery. The two other cases that bled died of causes other than bleeding, since bleeding had ceased in both. One patient died of intra-abdominal abscess associated with necrosis of the liver and obstructive jaundice secondary to a suppurative pancreatitis. The second patient died because of a lobar pneumonia uncontrolled by antibiotics. The red blood count was above 3.8 million, and the brownish, guaiac-positive vomitus which began four days after admission for hypertensive cardiovascular disease had all but ceased at the time of his death. Thus the mortality due to bleeding was .8%, one of the lowest figures that a reasonable perusal of the literature has as yet revealed.

The 123 admissions were broken down as to age as follows: 18% were between 20 and 29; 34% between 30 to 39; 5% between 40 to 49; 38% between 50 to 59, and 5% above 60. Age played a very minor part in the amount of blood necessary, the average for all age groups being close to 1,500 c.c. per patient. When it was realized that many of these ulcer patients had complicating conditions, a review of these factors was made. There were 41 complications, 29 of which were in the 50 to 59 year old age group, and of these 29, 19 resulted from hypertensive cardiovascular disease. Our figures regarding seasonal variation were consistent with those of other clinics reporting. There were 96 white and 27 Negro patients. There was no particular difference in the degree of anemia, the degree or duration of shock or subsequent surgery. Of the 123 admissions for duodenal ulcer that showed bleeding, 62% at some time during the bleeding period showed a red blood count below 3,000,000. These 77 bleeders required, on the average, 2,000 c.c. of whole blood. Based upon the initial physical examination and subsequent progress notes, a state of shock was present in only six cases. Ten cases, or 9.1%, showed hematemesis alone; 51, or 41%, only melena; 61 cases, or 41.9%, showed both. Seventy-four per cent of the cases gave a history of upper abdominal pain associated with the bleeding; 40% showed nausea, 40% vomiting, 25% weakness, 3% syncope, 3% dizziness, and 6% gave no symptoms at all except melena.

In the series all but two had had an x-ray diagnosis of ulcer. During 1947 to 1949, barium by mouth was given late in the course of bleeding, and thus the frequency of crater visualization was probably reduced. The number of craters demonstrated in this series totaled 44, or 35%. Those showing only deformity of the bulb totaled 85, or 69%. Some cases showed both deformity and crater. In the Negro race crater formation exceeded the average by 10%. Four of the six previously cited shock cases had ulcer with crater.

The incidence of cases of the entire group that had immediate or subsequent surgery was 19%. Five cases had had previous gastric surgery, one for perforation, three for gastroenterostomy, and one for exploration and drainage of a subphrenic abscess due to perforation. Emergency surgery because of uncontrolled bleeding was necessary in only two cases. One case, a 58 year old white male, had had uncontrolled bleeding for four days following admission. A Billroth number one was performed, and the diagnosis at operation was chronic perforation of a duodenal ulcer into the pancreas. The other was a 45 year old white male who continued bleeding for one month, during which time medical therapy included two units of plasma and 18 bottles of whole blood. A Billroth number two was performed. A duodenal ulcer penetrating into the pancreas was found. Operation had been delayed because of complicating nephrosclerosis, hypertension and arthritis. The patient had had two subsequent admissions for hema-

temesis and melena. No ulcers or varices could be demonstrated. It is of great interest to note, however, that of 121 cases treated medically, 46 cases, or 37%, were re-admitted for bleeding. Elective surgery was advised in 31 of these cases but seven refused, leaving 24 cases, or 19%, who had subsequent surgery following control of the bleeding. Only one patient continued to have gastric bleeding following resection.

Certain conclusions as a result of this analysis of 123 cases of bleeding

duodenal ulcers appear reasonable:

1. That the over-all mortality rate from bleeding duodenal ulcers compares very favorably with the results reported elsewhere.

That medical management of the bleeding period is adequate, emergency surgical intervention having been necessary in only two cases, or 1.6%.

3. That the percentage of recurrence of bleeding is 37% without surgery, and following elective gastric resection the percentage of further bleeding drops very significantly.

Gastric Ulcers: During the period of the study there were 22 admissions to the hospital with hemorrhage from gastric ulcer which was demonstrated either by x-ray examination or gastroscopy, or at autopsy. From our studies the incidence of bleeding gastric ulcer does not appear to be seasonal. The age incidence was highest in the 50 to 59 year old age group. There were four patients in the 30 to 39 year old age group. Of the 22 patients, three were Negro, 19 were white. It has been stated that hematemesis is more common in gastric ulcer and melena in duodenal ulcer. Fourteen of our patients had hematemesis and melena, only one patient had hematemesis without melena, and one patient had melena without hematemesis. The symptoms at the onset of bleeding were pain, nausea, vomiting and weakness, faintness or syncope. From the x-ray standpoint nine had gastric craters, two had prepyloric deformities, and one showed no demonstrable x-ray lesion but was found to have a gastric ulcer on gastroscopy. One was roentgenographically negative but, on subsequent re-admission, died in shock from hemorrhage. Autopsy showed a small crater in the pyloric end of the stomach. One patient in this group had an associated duodenal ulcer. There were other complications in this group: cardiovascular-renal disease (including cerebral vascular disease and hemiplegia) in eight patients, alcoholism in two, cirrhosis in two, subdiaphragmatic abscess in one and syphilis in one.

Treatment consisted principally of sedation, hourly or two-hourly feedings of boiled skim milk in accordance with patient's tolerance, antacids in some patients, intravenous fluids and blood replacement with repeated transfusions. Some patients were also placed on Wangensteen suction. Three patients did not require any transfusions. One patient died before any transfusion could be given. The remaining patients required from

two to 32 pints of blood each. There was no correlation between blood replacement and the patient's lowest blood pressure. Blood replacement was in inverse ratio to the hemoglobin level. For example, the patient who required 32 transfusions had an initial hemoglobin of 5 gm.

One patient had a gastric resection during his bleeding episode, with recovery. Four patients had elective gastric resections after the bleeding had been controlled by conservative medical means. Only one patient was re-admitted with a second episode of massive hemorrhage three years following the initial hemorrhage, and he died in shock three hours after admission.

Of this group of 22 patients, all but five recovered (a mortality of 22.3%). Of the five, only three died as a direct result of the gastric hemorrhage, resulting in a mortality of 13.6% due to bleeding per se. In this connection it might be stated that the mortality from hemorrhaging gastric ulcer is generally reported as twice that from duodenal ulcer. The mortality among men exceeds that among women. The two nonbleeding deaths were attributed to carcinoma of the liver with metastases and subdiaphragmatic abscess in one, and in the other a glioblastoma, pneumonia and perforation of a gastric ulcer with subphrenic abscess. The bleeding was controlled in both.

It is of interest that, to date, not one patient reported in this series has yet turned up with a gastric malignancy.

The salient points in the three cases that died of bleeding are as follows:

CASE REPORTS

Case 1. A 59 year old white male was admitted in shock with a hemoglobin of 8.5 gm. He was given six pints of blood and treated with gastric suction. He died in shock 48 hours later. Autopsy revealed cirrhosis with no varices, ulcer of the stomach with bleeding, lobar pneumonia and suppurative pericarditis.

Case 2. A 79 year old white male was re-admitted in shock, with massive hematemesis and melena, three years after a previous episode of gastric hemorrhage from which he had recovered. He remained in shock three hours, during which time he was treated with plasma and saline. Blood arrived after the patient died. Autopsy showed a small crater in the pyloric end of the stomach.

Case 3. A 58 year old Negro male was admitted with homologous serum jaundice. On the thirteenth hospital day he suffered a profuse hemorrhage from the stomach and died on the sixteenth day with continuing hemorrhage. Autopsy showed an acute ulcer of stomach near the esophageal junction with massive hemorrhage, infectious hepatitis, cholelithiasis and acute interstitial nephritis.

Prolapsed Antral Mucosa: Since 1946 there have been 10 admissions for bleeding ascribed to prolapsed antral mucosa. The ages have varied between 23 to 55, with one patient having five admissions. One of these patients was a Negro, the remainder were white. The one patient with five admissions was initially in this hospital at the age of 47 for duodenal ulcer with hemorrhage and was found to have persistent deformity of the duodenal cap. He was again admitted in 1946, at the age of 52, with

the x-rry report of coarse, irregular mucosa in the cardia and pars media, and apical deformity. In 1947 he was admitted for melena, and x-ray at that time revealed a prolapse of the mucosa of the pyloric ring into the duodenum. No ulcer crater was noted. He was re-admitted for bleeding in January, 1948, April, 1948, and September, 1948, at which time he refused surgery. He was re-admitted in February, 1949, for melena. This time a gastrointestinal series revealed a small pouch arising from the lesser curvature side of the stomach, just above the angle, which was considered to be a gastric ulcer. The prolapse was again noted with associated antral gastritis. Subsequent gastrointestinal series after medical treatment revealed healing of the gastric ulcer but slight increase in the degree of prolapse. On March 21, 1949, laparotomy was done and a healed ulcer was noted on the anterior surface of the stomach close to the greater curvature. There was prolapse of the pyloric mucosa about one inch into the duodenum, and an anterior Hofmeister operation was done. He has had no further re-admissions to the hospital. We cannot be certain that he had

not bled from his gastric ulcer.

Site of Bleeding Unknown: In most reported large series of gastrointestinal hemorrhage there are usually 10 to 15% in whom no site for hemorrhage can be found. The incidence varies in different series, and figures as low as 2% and as high as 30% have been reported. In our series there were 13 patients in whom a definite diagnosis as to the site of bleeding could not be given. Three of these cases were Negro and the remainder were white. Seven of these patients gave a fairly good history which clinically might have been consistent with peptic ulceration. However, x-ray examination failed to reveal any definite lesions. There was one death, a 60 year old white male admitted for hematemesis, melena and weakness. His initial red blood count was 2,500,000, with 8 gm. of hemoglobin. His basic condition was coronary arteriosclerotic and hypertensive heart disease, and he had an acute posterior wall infarction. He died two months after admission, at which time his red blood count was 4.3 million, and he was not considered to be a "bleeding" death. Two patients had had previous subtotal gastrectomies prior to admission for bleeding and no anastomotic ulcer was found. It is to be noted that all these patients were seen only once, and no subsequent follow-up studies are available. There are many pitfalls in the evaluation of the patient with upper gastrointestinal bleeding. Great clinical acumen and painstaking efforts are required to reduce this minimum of nondiagnosed sites of bleeding.

There were three cases of carcinoma of the stomach admitted for hemorrhage, and there were three deaths in this series. The cirrhotics did poorly. The mortality was high, due mainly to liver failure precipitated by hemorrhage. The control of bleeding apparently meant little in terms of survival.

Medical therapy has varied slightly from time to time during the last several years. However, basically it consists of the following:

1. Absolute bed-rest and quiet.

2. Sedation with drugs other than morphine, to avoid nausea and vomiting, and, in those not vomiting, the starting of a progressive ulcer regimen. Rarely has a patient been on a food-abstinence regimen. Feedings have been given every one to two hours during the day and also every two hours through the night. Where food has not been given through the night, antacid powders or Amphojel has been given. Usually, however, the antacid has consisted of calcium carbonate rather than Amphojel. Blood loss has been replaced with blood transfusions. Careful attention to hematocrit, blood pressure, electrolytic balance and urinary output has been a necessary feature of our regimen. Avoidance of circulation overload has also been of paramount importance in the elderly, arteriosclerotic patient.

3. The Blakemore-Sengstaken esophageal tamponade tube has been used in bleeding due to esophageal and gastric varices associated with portal hypertension. This has almost invariably controlled bleeding, though, as mentioned previously, it had little bearing on the ultimate survival in view of the frequently ensuing liver failure and coma.

SUMMARY

Two hundred admissions for gastrointestinal hemorrhage have been analyzed. Of these, 123 were due to duodenal ulcer, 22 to gastric ulcer. There were three deaths in the duodenal ulcer group but only one directly attributable to blood loss. The corrected mortality in this group was accordingly .8%.

We feel that medical therapy has resulted in a mortality rate significantly lower, by far, than the best reported with surgical intervention. Emergency surgical intervention was necessary in only two cases.

Of the 22 patients with gastric ulceration, three died as a direct result of gastric hemorrhage, a mortality of 13.6%. This figure is significantly higher than that due to duodenal ulcer, and is in keeping with our current concept of earlier surgical intervention in patients with bleeding gastric ulcers.

SUMMARIO IN INTERLINGUA

Esseva analysate 200 casos de hemorrhagia del tracto gastrointestinal superior. Le casos seligite habeva un numeration erythrocytic de non plus que 3,5 milliones o minus que 10 g de hemoglobina. Le serie includeva 122 casos de ulceration duodenal, 22 casos de ulcere gastric, 29 casos de cirrhosis del hepate con varices esophagee, 10 casos de prolapso de mucosa antral, e 3 casos de malignitate gastric. In 13 casos le sito del sanguination esseva indeterminate.

Circa un in quatro casos de ulceration peptic del duodeno resulta in sanguination, sed ulceration gastric ha un plus alte incidentia de hemorrhagia e un plus alte mortalitate.

Solmente tres del patientes con ulceres duodenal moriva. Solmente un de iste tres mortes esseva effectuate per hemorrhagia. Le patiente in question habeva essite hospitalisate con symptomas e signos de perforation e abscesso. Un abscesso

subphrenic esseva drainate, sed il occurreva un sanguination postoperatori, e le patiente moriva. Le autopsia revelava un ulcere duodenal con erosion a in le arteria pancreatico-duodenal. Assi le mortalitate debite a sanguination de ulcere duodenal amontava a 0,8%.

Le tractamento del casos hic presentate esseva le responsabilitate de plure differente membros del personal. In principio le tractamento consisteva de transfusiones de sanguine, allectamento, e alimentation per bullite lacte discremate o per un modificate dieta de Meulengracht. Durante le nocte le patientes recipeva lacte con o sin carbonato de calcium a intervallos de duo horas si longo como le feces continuava esser nigre. In plus illes recipeva antispasmodicos e sedativos nonnarcotic.

Un intervention chirurgic esseva necessari in duo casos de sanguination nonsubjugabile. Ambe iste patientes superviveva.

Le valores del mortalitate in iste serie se trova de accordo con le plus favorabile statisticas reportate in le tractamento medical de sanguination de ulceres duodenal. Le valores es melior que illos reportate in le tractamento chirurgic de iste condition.

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LIPOGRANULOMATOUS PSEUDOSARCOID*

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Boeck's sarcoid, or true sarcoidosis, has been defined as a disease of unknown etiology, characterized pathologically by the presence in any organ or tissue of epithelioid cell tubercles with absent or inconspicuous necrosis. Refractile and apparently calcified bodies are frequently present in the giant cells of the tubercles, but acid-fast organisms are absent. The characteristic microscopic granulomas persist, although the lesions become scarred and hyalinized.

Many investigators have observed that there are a variety of agents which evoke a pattern of tissue reaction similar to the lesions seen in Boeck's sarcoid.1-4 Among these agents are acid-fast bacilli, including Mycobacterium tuberculosis and Mycobacterium leprae, helminths, fungi, including Histoplasma capsulatum,5 brucella, foreign bodies, lipids, beryllium and silicon. The diagnosis of sarcoid is therefore often made by exclusion, after eliminating the possibilities listed as etiologic factors. The wide use of the term "sarcoid" as a generic designation for any tuberculoid granulomatous reaction and the emphasis on the nonspecificity of the reaction have not been helpful in advancing our knowledge of true sarcoidosis. A poorly understood entity can be clarified only by study of a homogeneous group of patients. It is therefore suggested that the diagnosis of sarcoid be limited to instances in which classic lesions are encountered in patients with the classic clinical syndromes, and that attempts be made specifically to characterize and separate those lesions which simulate sarcoid.

There is little argument about the necessity for designating as tuberculosis the sarcoid-like lesions due to tubercle bacilli, or for diagnosing as beryllium granulomas the tissue reactions produced by beryllium which so closely resemble sarcoid. The granulomas which result from the deposition and phagocytosis of lipids, and which strikingly resemble sarcoid lesions, have not been so clearly delimited, although they have been well known for years.

Granulomas which develop in relation to deposits of lipid can be classified as endogenous or exogenous, according to the origin of the lipid, and diffuse or focal, according to the distribution of the granulomas (table 1).

^{*} Received for publication March 2, 1956.

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Presented before the Section on Pathology and Bacteriology at the 83rd Annual Session of the California Medical Association, Los Angeles, May 9-13, 1954.

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Examples of exogenous lipogranulomas are the pulmonary granulomas following the aspiration of mineral oil. Endogenous lipogranulomas are found in diseases with disturbances of lipid metabolism, hyperlipemia and fatty deposits. We have encountered them in diabetes (figures 1, 2 and 3), nephrotic syndromes and myxedema, and they have been reported in pernicious anemia. Examples of focal lipogranulomas are those seen in lymph nodes draining tumors; the granulomas seen in germinomas of the ovary and testis are probably not ordinary lipogranulomas, since these tumors are not rich in fat. Diffuse lipogranulomas are those which are systemic in distribution and may involve the lung, hilus nodes, spleen, liver (figure 4) and marrow (figure 5). It is this category in particular which may simulate sarcoidosis.

TABLE 1

Lipogranulomatous Pseudosarcoid

Localized form (focal lesions and/or draining nodes; spleen)

Endogenous lipoid

Hematomas

Tumors

Cholesterol deposits

Xanthoid lesions

Fat embolism

Fat necrosis

Exogenous lipoid (mineral oil, fecal fat, etc.)

Aspiration pneumonia

Regional enteritis

Ulcerative colitis Parenteral injection

Generalized form (lung, nodes, liver, spleen, marrow)

Localized form with dissemination

Disturbed lipid metabolism

Myxedema

Diabetes

Nephrotic syndromes

Pernicious anemia

We have encountered lipogranulomas most commonly as an incidental finding in spleens removed at autopsy (figure 6) and in lymph nodes removed at cholecystectomy (figure 7). The lipogranulomas in these locations can be attributed to the absorption of substances such as mineral oil. Stryker ¹⁶ demonstrated absorption of mineral oil from the human intestine. He found the oil in mesenteric lymph nodes, spleen and liver, and observed that the oil is a foreign body in the tissues, exciting a typical inflammatory reaction, with oleophages and chronic inflammatory cells.

To determine the frequency of such lipogranulomas, the spleens from 264 consecutive autopsies and the gall-bladders in a series of 6,148 surgical specimens were examined. This material comprises the autopsies and surgical specimens at the Cedars of Lebanon Hospital during the year 1952.

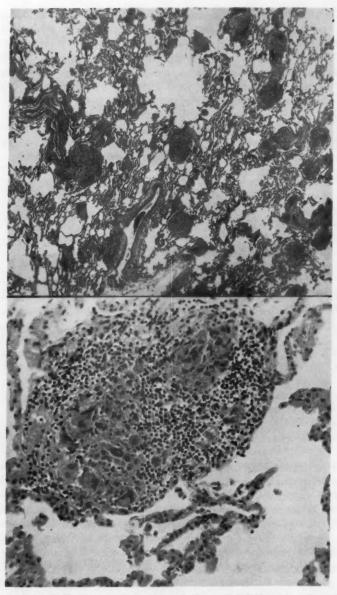


Fig. 1. (above) Pseudosarcoid granulomas in lung of diabetic patient (Los Angeles County General Hospital). × 20.

Fig. 2. (below) Pseudosarcoid granulomas in lung of diabetic patient. High power view (Los Angeles County General Hospital). × 175.

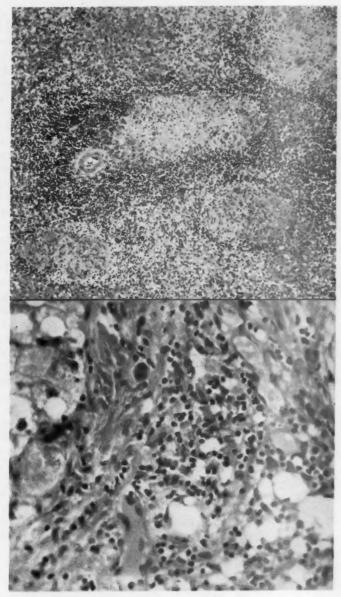


Fig. 3. (above) Pseudosarcoid granulomas in spleen of diabetic patient with pulmonary lesions (Los Angeles County General Hospital). × 100.

Fig. 4. (below) Lipogranuloma in portal triad of liver. History of ingestion of mineral oil. × 360.

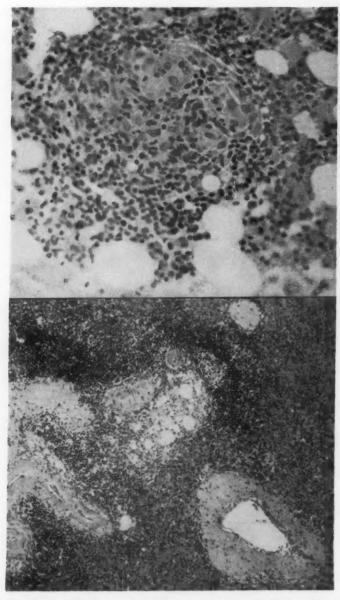


Fig. 5. (above) Pseudosarcoid granuloma in bone marrow. Patient had multiple old fractures and a history of ingestion of mineral oil. × 350.

Fig. 6. (below) Lipogranuloma in characteristic location near splenic follicular arteriole. × 100.

In the year's autopsy material, 17 instances of lipogranulomas in the spleen were found, constituting an incidence of 6%. Three of these patients were diabetics. During the year 1952 a total of 267 gall-bladders were removed. In 31 of these gall-bladders a lymph node was found attached to the specimen adjacent to the cystic duct. This node, one of a group of three to six hepatic nodes, is constant in location and is found near the junction of the cystic and hepatic ducts. The 31 lymph nodes found were examined microscopically. In 22 of them there were lipogranulomas, representing an incidence of 71%.

In studying lipogranulomas, we have seen three stages of development (figures 8, 9, 10 and 11): (1) a stage in which the oil droplets occur as clusters of variable size; (2) a stage in which there are clusters of oleophages or lipid histiocytes and giant cells, with easily recognizable large and small sized droplets (in contrast to the foamy dispersion of intracytoplasmic lipid of xanthoma cells); ²² (3) a stage in which there are coalescent lipid histiocytes, giant cells with or without asteroids, and epithelioid cells, with formation of noncaseating epithelioid tubercles.

It is the final stage of the lesion which mimics Boeck's sarcoid and should therefore be called pseudosarcoid. When frank lipid has entirely disappeared, adjacent granulomas containing recognizable oil droplets may

provide the only clue to the etiology of the lesion.

The presence of asteroids (figure 12) may be taken as evidence of antecedent lipoid deposits.^{6,7} The asteroids, star-shaped radial inclusions, and the contoured laminated Boeck-Schaumann's bodies, both found in the giant cells of tuberculoid granulomas, have attracted considerable interest.^{6,8-11} In the past the finding of asteroids had been considered diagnostic of sarcoid in some laboratories, but they are no longer regarded as disease-specific.

In addition to sarcoidosis, asteroid bodies have been found in the following conditions: ^{0,8,9,10,11} (1) in lymph nodes draining tumors and in the neoplasms themselves; (2) in tendon sheath xanthoma; ¹² (3) in leprosy; (4) in foreign body reactions, including reactions to suture material, deposits of sodium urate crystals, ectopic hair, sebaceous material and keratin debris; (5) in cholesterol deposits and hematomas; (6) in irradiated tissues; ¹³ (7) in lymph nodes and lymphatics draining regional enteritis and ulcerative colitis; (8) in fat necrosis and fat embolism; (9) in pseudo-Whipple's disease; (10) in plasma cell myeloma; ¹⁴ (11) in Gaucher's disease. ¹⁴

Hirsch,^{6,7} in his studies of lipogranulomas and asteroids, concluded that the bodies are crystalline forms of fats solid at body temperature, separated from an oil system containing cholesterol. He further concluded that the crystals form in a liquid fat system by the usual laws governing crystallization. He produced rosette bodies resembling asteroids by intravenous injection of a mixture containing a lipid extracted from human fat, cholesterol and stearin or palmitin. Ricker and Clark ¹⁵ noted the association

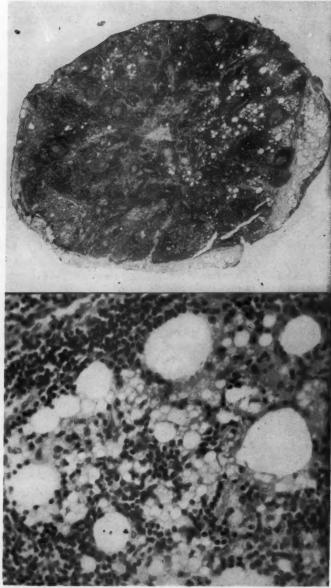


Fig. 7. (above) Low power view of hepatic node showing fatty vacuoles of lipogranulomas. × 20.

Fig. 8. (below) Early stage in formation of pseudosarcoid. Considerable fat present × 100.

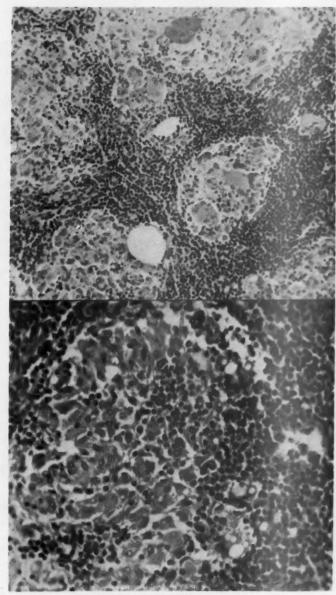


Fig. 9. (above) Pseudosarcoid lipogranuloma in hepatic lymph node. Large fatty vacuoles still present. × 175.

Fig. 10. (below) Pseudosarcoid lipogranuloma in hepatic lymph node consisting of epithelioid cells with fatty material almost gone. × 360.

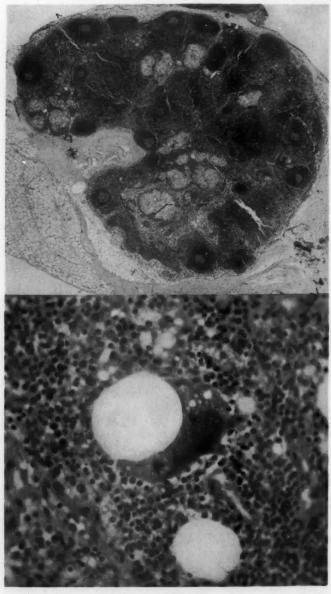


Fig. 11. (above) Low power view of hepatic node showing pseudosarcoid granulomas. Little fat remains. × 20.

Fig. 12. (below) Giant cell with asteroid in relation to fatty vacuoles in hepatic node. × 360.

of intracytoplasmic stainable lipid in an occasional case of sarcoidosis, but these authors were using the designation "sarcoid" in the loose sense. In a more recent study Jaques has concluded that, on the basis of staining reactions and solubility, the inclusions may be lipoprotein. Engle ° crys-

tallized asteroids from solutions of extracted lipid.

The possibility remains that sarcoid may be a variant of the lipogranulomatous reaction. Jaques ¹¹ and Refvem ⁴ have emphasized the rôle of phospholipids in the pathogenesis of sarcoid and sarcoid-like lesions. It may prove worth while to study mycolic acid in relation to these diseases. The tuberculoid sperm granulomas described by Friedman and Garske ¹⁹ have since been shown by Berg ²⁰ to be related to an acid-fast lipid of spermatozoa. This lipid, in its absorption spectrum and tissue reactions, resembles mycolic acid, a substance also found in tubercle bacilli. Germinomas should be analyzed for mycolic acid, since it might be a factor in the formation of the granulomas seen in these tumors of the testis and ovary.

Jaques 2 has also emphasized that generalized sarcoidosis must be differentiated from focal sarcoid lesions. However, some of the obviously lipogranulomatous lesions which we have studied and believe he would designate as focal sarcoids have been disseminated and have involved lung, hilar nodes and even marrow. Mallory 21 found little evidence of sarcoidosis either clinically or at autopsy in some of his examples of pulmonary fibrosis and granulomatous pneumonitis. They clearly fall into the category proposed by the present study. Refvem 28 suggested that some patients usually diagnosed as instances of sarcoidosis might represent another entity, although he thought that mineral particles rather than fat might be involved. The appearance of pulmonary radiographs in instances of the generalized form of lipogranulomatous pseudosarcoid is occasionally identical with that of sarcoidosis. We have seen a number of lipogranulomas in the portal triads of patients with cirrhosis. It has not been clear whether these were simply due to accumulation of mineral oil or other lipoid which was enhanced by the lymphatic stasis associated with cirrhosis, or whether the fatty diastemata associated with cirrhosis provoked a lipogranulomatous reaction.

SUMMARY

The diagnosis of sarcoid is sometimes made when some generic designation such as tuberculoid granuloma or pseudosarcoid granuloma might be more appropriate. In studying sarcoid-like granulomas of this sort a number appear to be lipogranulomas. This is especially true of those associated with asteroid bodies in the giant cells. Although occasional instances are seen in patients with disturbances of lipid metabolism, the lesions are most commonly encountered in spleens at autopsy and in hepatic lymph nodes removed at cholecystectomy. These may be due to absorption of oil from the intestine. The lung and hilar lymph nodes, the liver, marrow

and mesenteric nodes may also be involved. All stages from frank lipid histiocytosis to the granuloma simulating sarcoid can be demonstrated. Because the fat disappears in the final stage the nature of the lesion is often not recognized. In a study of sarcoid, the lipogranulomatous pseudosarcoids must be recognized and eliminated from consideration, unless eventual discovery of the true nature of sarcoidosis proves that it too is a lipogranuloma. It is suggested that the term "sarcoidosis" be reserved for classic cases, and that the term "pseudosarcoid" with an appropriate prefix be used for other conditions, e.g., lipogranulomatous pseudosarcoid, beryllium pseudosarcoid, helminth pseudosarcoid, etc. Studies of skin sensitivity to mycolic acid in patients with sarcoid might prove interesting.

ACKNOWLEDGMENT

Photomicrographs by Dale Gillette. Dr. Henry Glover aided in this study.

SUMMARIO IN INTERLINGUA

Varie agentes es capace a evocar historeactiones simile o identic con le lesiones de sarcoide de Boeck. Iste agentes include bacillos acido-resistente, fungos, helminthos, beryllium, silicium, e lipidos. Proque le etiologia de sarcoide de Boeck non es cognite, le uso del parola sarcoide como termino generic pro omne granuloma tuberculoide ha essite pauco avantageose in le characterisation e delineation de sarcoide de Boeck. Per consequente il es importante separar accuratemente le granulomas que simula sarcoide. Nos ha usate le termino pseudosarcoide, precedite per un appropriate epitheto pro designar le etiologia de un specific typo de granuloma, como per exemplo in 'pseudosarcoide lipogranulomatose.' Le pseudosarcoides que resulta del deposition e del phagocytose de lipidos ha essite cognoscite durante multe annos, sed illos non ha essite delimitate tanto clarmente como altere granulomas de apparentia simile a sarcoide. Pseudosarcoides lipogranulomatose pote esser classificate como exogene (aspiration de oleo mineral) o endogene (statos hyperlipemic) e como localisate (lesiones focal) o generalisate (pulmone, nodos, hepate, splen, e medulla). II es particularmente le lipogranulomas generalisate o systemic que simula sarcoide de Boeck. In autopsias routinari e specimens chirurgic, lipogranulomas es communmente incontrate in le splen autopsiate e in le nodos lymphatic attachate al ducto (nodo hepatic) de chirurgicamente abferite vesicas biliari. Nos ha vidite tres stadios de disveloppamento in iste lesiones, comenciante con racemos de guttettas de lipido de varie dimensiones e progredente a granulomas tuberculoide componite de coalescente histiocytos lipidic, cellulas epithelioide, e cellulas gigante, con o sin asteroides. In le stadio final, lipido pote disparer completemente, de maniera que le sol indicio etiologic es granulomas adjacente que contine recognoscibile guttettas de lipido. Alora le differentiation histologic inter pseudosarcoide lipogranulomatose e sarcoide de Boeck pote devenir impossibile. Le presentia de asteroides non es un characteristica specific de ulle morbo. Asteroides pare esser alterate lipido, probabilemente lipoproteina.

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SPACED FAT FEEDING: A REGIME OF MANAGE-MENT FOR FAMILIAL HYPERLIPEMIA *

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It seems desirable to present this paper at this time in order to describe a régime of treatment for familial hyperlipemia. We feel that if we waited until our current investigation into the genetic and metabolic aspects of familial hyperlipemia was ready for publication, a very satisfactory and practical method of treating these patients would be withheld from the profession longer than would be desirable.

This régime has been presented orally a number of times from 1948 until the present. The use of it, however, is not widespread, and there does seem to be a need for such an effective and simple method of control.

Familial hyperlipemia was first described in 1932 by Buerger and Grütz and appeared to be a rare disease, since it was reported only when the complete syndrome was present. Only 40 cases have been reported to date in the literature.2 It is our present belief that this condition as reported represents the homozygous abnormal. We feel that the heterozygous abnormal is far more common than is generally believed, and frequently overlooked. Data we have at present support this genetic concept. We are in the process of collecting more data and will withhold publication until we can offer substantial proof of a mode of inheritance, rather than merely support a hypothesis.

For the sake of this article, the hypothesis can be stated as follows:

1. The basic metabolic defect in familial hyperlipemia is a retarded removal of ingested fat from the blood stream after normal absorption (figure 1). This is usually the only abnormality found in the heterozygous abnormal. The homozygous abnormal is further complicated by hepatosplenomegaly, abdominal crises and, frequently, secondary xanthoma.3

2. The mode of inheritance is that of an incomplete dominant, such as essential familial hypercholesterolemia,4 but the penetrance is probably not so high.

3. Over a period of years the fat gradually accumulates in the blood stream by a series of small, steplike increments, because the postprandial elevation of fat never returns to the fasting level before another fat meal is ingested (figure 2). The elevated cholesterol is secondary and can be controlled if the hyperlipemia can.

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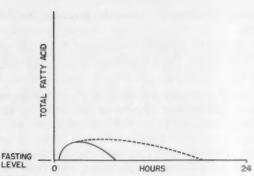


Fig. 1. The solid line indicates a usual fat tolerance test in a normal individual, while the broken line indicates the delayed removal of fat found present in a person with familial hyperlipemia.

That we can usually control this hyperlipemia we are convinced; and, even if additional data cause us to modify our working hypothesis, it will have no effect on the efficacy of the method of control.

At this point the reader may well ask, "Why the emphasis on the control of this condition?" It has been stated in the past that familial hyperlipemia is not associated with an increased incidence of atherosclerosis.⁵ This is disputed by Malmros, Swahn and Truedsson ⁶ and Soffer and Murray.⁷

We, too, have the firm conviction that uncontrolled familial hyperlipemia is associated with an increased incidence of atherosclerosis, and that the incidence of the heterozygous form is much higher than is generally believed. If this is the case, it is important to control this condition and to establish this control early in life, with the expectation of preventing the acceleration

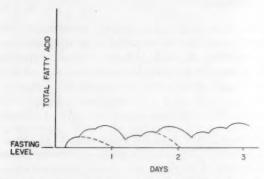


Fig. 2. Here, shown diagrammatically, is the slow build-up of fat in the blood stream due to the fact that the fasting level is not reached before the next fat meal is ingested. The broken lines indicate how the removal of the fat from the blood stream might continue, had not another meal of fat been superimposed upon the elevated blood fat. What is shown here in exaggerated fashion continues over the years to build up hyperlipemia and hyper-cholesterolemia.

of the atherogenic process and, if possible, reversing the process in established atheroma.

With this concept of delayed removal and a steplike accumulation of lipids in the blood stream, the following method of control becomes logical and self-evident:

1. Reduction of the existing hyperlipemia and the secondary elevation of cholesterol and phospholipid by rigid fat restriction for such a time as is necessary to bring the blood lipids within accepted "normal limits."

2. Maintaining the blood lipids within such limits, by properly spacing the ingested fat in time so that, even with the slow removal rate, the post-prandial hyperlipemia will return to the fasting level (now "normal") before another fat meal is ingested (figure 3).

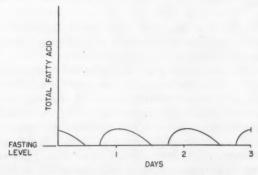


Fig. 3. This shows, diagrammatically, when the spaced fat régime is used, how the blood fats return to the fasting level before the next fat meal is ingested, even though the removal rate is prolonged.

This means that after the period of rigid fat restriction, the usual patient with familial hyperlipemia can be controlled with a régime consisting of a fatty meal not more than once each 24 hours. Usually this amounts to a fat-free breakfast, a fat-free lunch and no restriction whatever on the evening meal. Of course, if the patient prefers to have his heavy meal in the middle of the day, he may do so and have a fat-free meal at night.

A régime such as that described above has many advantages:

- 1. It is not hard to follow from the patient's point of view.
- 2. It does not restrict the patient's social intercourse by making him appear different because of his diet.
- 3. It does not rule out "snacks," provided they are fat-free (i.e., fruit, skimmed milk, etc.).
- 4. Should the patient break the régime because of business or social pressures, and the fat spacing be interfered with, this can be corrected by a

period of rigid fat restriction equal in time to the fat "binge," followed by a return to the spaced fat program.

Our patients have responded well to this type of management, and at present we have several that we have followed for periods of four years or longer (one for seven years). They have not had to modify their way of life drastically. Most have broken over for one reason or another, but control has been reëstablished by the method described in (4) above. Some of these breaks in control have been for relatively long periods, such as a trip to Europe.

In our laboratory we do a fat tolerance test on each case studied, but such an expensive and time-consuming procedure is not necessary in private practice. The fat tolerance test, as used by us, consists of a meal containing 85 to 90 gm. of either dairy or vegetable fat, followed by periodic blood lipid fractions and alpha and beta lipoprotein determinations done over a period of 30 hours.

This is not the place to report the therapeutic results of the control of hyperlipemia, as we do not have sufficient data to evaluate critically a large enough number of cases, either with or without symptoms, over a long enough period of time. We have, however, observed lessening of severity and even disappearance of angina pectoris, as well as the disappearance of xanthoma secondary to the hyperlipemia.

As was mentioned above, the fat tolerance test is expensive and almost requires the facilities of a research laboratory. While desirable and even necessary in a study such as we have under way, it is not a necessary step in the management of hyperlipemia. For practical purposes the following steps have proved of value to acquaintances and former students of ours in their private practice:

1. Fasting blood drawn for any test is inspected by the physician after the plasma or serum has separated from the red blood cells or clot. If it is milky or shows any tendency in that direction, a cholesterol and/or total fatty acid is done. If these are elevated, after other causes of hyperlipemia have been ruled out, i.e., hypothyroidism, diabetes, etc., it is assumed that the patient has familial hyperlipemia.

2. The patient's fat intake is rigidly restricted for 30 days and the determinations referred to above are repeated. If they are normal, the spaced fat régime is started. If they are not normal, the period of rigid fat restriction is continued for another 30 days and even an additional 30. If at this time the blood cholesterol and/or fatty acids have not returned to normal, the cause of their elevation can be assumed not to be due to familial hyperlipemia.

3. The physician assumes that the patient can clear the blood stream of a fat load in less than 24 hours, since approximately 75% of the patients

we have studied so far do so, and a 24-hour spacing of ingested fat is inaugurated.

4. If after several months the blood lipids are again increased, rigid fat restriction is again started and, after a return to normal of the blood lipids, the patient is placed on a régime where the ingested fats are spaced 48 hours apart.

The above simplified régime would have been adequate for the large majority of patients we have studied to date. It has, of course, the inevitable drawbacks encountered when a relatively precise research technic is modified so that it is practical as an office procedure. If blood cholesterol is the only lipid determination that can be done, it may not be easy to distinguish familial hyperlipemia from essential familial hypercholesterolemia, and we have shown that fat restriction has no effect in this latter condition. ^{8, 9} This differentiation is particularly hard if there is little visual evidence of hyperlipemia, as may occur in younger individuals.

Some sera, for reasons as yet unknown to us, appear lipemic (opalescent) but, on analysis, show no elevation in total fatty acids. The lipemia associated with renal disease is sometimes difficult to identify and, even if controlled, is of little consequence in light of the ominous sequelae of the renal disease (i.e., hypertension, uremia, etc.). While the hypercholesterolemia and/or hyperlipemia of myxedema (or, more commonly, hypothyroidism) is viewed with alarm and, to a degree, can be corrected with diet, the main problem is the decreased thyroid function, and dietary management is no substitute for hormonal treatment. Hyperlipemia secondary to diabetes can also be corrected, to a degree, by diet; but one would not be justified in withholding insulin for a dietary approach, since control of the primary metabolic defect with insulin usually corrects the hyperlipemia.

The procedure outlined above is far from perfect, but is useful, effective and practical.

An additional way in which the spaced fat régime may be used should be commented on. As one grows older, the time or rate of fat clearance from the blood stream may, and usually does, increase. Prophylactically, a fat-free breakfast after a certain age may be desirable, and we arbitrarily select 40 to 45 years of age. A fat-free breakfast is not distasteful and may prevent increased atherogenesis, at worst, or induce regression of preformed atherosclerosis, at best.

DISCUSSION

The régime presented is not a panacea. It will not be equally effective in all cases of hyperlipemia. It does, however, seem to offer a therapeutic procedure that effects chemical changes in the blood that, at least theoretically, are desirable. It does not supplant the need for careful and meticulous work-up of a patient; rather, it is dependent on it. While not perfect, it offers a method of treatment that may be of value and has to a limited degree

proved so. It also offers a method of prophylactic therapy that prevents chemical changes in the blood lipids currently thought to be undesirable.

SUMMARY

- 1. A hypothesis to explain the genetic mode of transmission of familial hyperlipemia has been stated.
- 2. This hypothesis has been enlarged to include a possible way that the basic metabolic error in familial hyperlipemia may act to produce a combination of hypercholesterolemia and hyperlipemia.
- 3. A practical, simple and effective régime for the control of what is believed to be a not uncommon metabolic defect has been described.
- 4. The normal delayed postprandial fat clearance associated with advancing years has been discussed.

SUMMARIO IN INTERLINGUA

Per un appropriate intervallation del consumption de grassia il es possibile mantener normal nivellos de cholesterol, phospholipidos, e total acidos grasse in patientes de hyperlipemia familial post que le nivellos sanguinee de iste substantias ha essite reducite a valores normal per un stricte curso de 30 dies de restriction del ingestion de grassia. Super le base del inspection visual de sero o plasma nos crede possibile le identification de circa 75% del heterozygotic hyperlipemicos familial in stadios precoce sin le uso del test del toleration de grassia.

Le regime ha le avantages (1) que illo es facile a observar ab le puncto de vista del patiente, (2) que illo non restringe le "vita social" del patiente per render le "differente" a causa de su dieta, (3) que illo non elimina le possibilitate de parve collationes inter le repastos, e (4) que inevitabile violationes del regime es facile a corriger.

Es presentate un hypothese pragmatic del modo de transmission genetic e del defecto metabolic de hyperlipemia familial. Iste hypothese include le conception que le modo heterozygotic del condition es non del toto infrequente ben que illo es clinicamente minus dramatic que le modo homozygotic.

Proque personas de etate plus avantiate pare esser characterisate per un tendentia de effectuar le clearance de grassia minus efficacemente que personas plus juvene, le regime hic recommendate es possibilemente etiam usabile como mesura prophylactic in le population vetulante.

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CASE REPORTS

"REVERSED COARCTATION": REVIEW OF PULSELESS DISEASE AND REPORT OF A CASE * †

By ALVA BOWEN WEIR, JR., M.D., and J. WARREN KYLE, M.D., Memphis, Tennessee

UNTIL recently "pulseless disease" has been almost completely ignored in American and British literature. It has long been recognized by the Japanese and, more recently, by the Scandinavians, but journals published in this country have contained only rare, isolated case reports or casual mention of the condition until the last two years.

"Pulseless disease" may be defined as a chronic disorder of the great arteries which branch from the aortic arch, or of their ostia, which results in diminished caliber or obstruction of the lumens of those vessels, thus causing diminished or absent pulsation in the arteries of the head, neck and upper extremities.

Though somewhat descriptive, the term "pulseless disease" is neither entirely accurate nor sufficiently specific as a name for the disorder under discussion. Many other terms have been applied (table 1). Probably the most nearly perfect is "chronic subclavian-carotid obstruction syndrome."

An intriguing term is that of "reversed coarctation," used by two authors,1,2 and included in the title of this paper partly to gain attention and partly as a descriptive term. This term has been criticized by several authors as misleading and inadequate. It is applicable, however, in two respects in implying the clinical picture. First, there is a pattern of collateral arterial circulation as is seen in coarctation of the aorta, but for the reverse reason and with blood flow in the opposite direction. Enlargement of collateral circulation through intercostal arteries, internal mammary arteries, and about the scapula is for the purpose of getting blood to the head, neck and upper extremities rather than to the trunk and lower extremities. Consequently, flow is from aorta into intercostal arteries to internal mammary arteries to the upper portion of the body, rather than from internal mammary to intercostal arteries to aorta to the lower portion of the body. Second, "reversed coarctation" is applicable terminology in that, with low or absent pulse pressure in the upper extremities, there is frequently hypertension in the lower extremities. Nevertheless, "reversed coarctation" is not an accurate term and is not recommended for general use.

"Takayasu's disease" has been the popular term in Japan because of a report and review by a physician of that name in 1908.3 It seems that more cases have

^{*} Received for publication February 13, 1956.

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† Presented at the Kentucky-Tennessee Regional Meeting of the American College of Physicians, November 6, 1955.

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been reported in Japan than in the rest of the world combined. The term "aortic arch syndrome(s)" was used in a Scandinavian article 4 in 1946, and was adopted as the preferable term by Ross and McKusick in their review 5 in 1953. They included in their review and discussion, however, instances of occlusion of only one or more, rather than all, branches of the aortic arch. In a consideration of these less complete forms of "pulseless disease," such older terms as "anisosphygmia," "pulsus incongruens" and "pulsus differens," as mentioned by Ross and McKusick, may also be included.

HISTORY

The earliest case of obliteration of pulses in the neck and both arms to which an allusion could be found in reviews of this subject is that of an officer who had fought at Waterloo (Davy, J., in ⁵). There he was severely wounded in the chest, and some years later had no pulse anywhere along the course of the great vessels arising from the aortic arch. Postmortem examination showed a large aneurysm which is now presumed to have been syphilitic in etiology and probably

TABLE 1

Many of the Terms Which Have Been Applied to the Chronic Subclavian-Carotid Obstruction Syndrome

Terminology

Pulseless disease Chronic subclavian-carotid obstruction syndrome Reversed coarctation Takayasu's disease Thromboarteritis obliterans subclaviocarotica Brachiocephalic arteritis

Aortic arch syndromes Anisosphygmia Pulsus incongruens Pulsus differens

unrelated to the chest trauma incurred at Waterloo. A similar case was reported in 1872 (Parsons, C., in ⁵) in an American Civil War veteran whose symptoms had begun four years following a battle-incurred chest injury. Since then there have been a few other isolated case reports of aneurysmal etiology of absent pulsations in all of the four large vessels. Osler mentioned it in 1908.⁶ Kampmeier and Neumann reported a case in 1930.⁷

As previously stated, the eponymic designation "Takayasu's disease" resulted from a report in 1908 by a Japanese author of that name. His was a syndrome characterized by a loss of radial artery pulsations, absence of detectable blood pressure in the upper extremities, and eye findings, including retinal lesions and cataracts. Photopsia, blurred vision and attacks of syncope frequently associated with convulsions were the most common presenting symptoms. Most patients were young females. The etiology was considered to be a panarteritis of unknown cause. Microscopically the lesions of the involved arteries were suggestive of tuberculosis. A tabulated summary of cases reported by Japanese authors was included in the report by Caccamise and Whitman in 1952 s in this country, and they included a case which they considered the first to be reported outside

Japan. Undoubtedly they were separating this quasi entity of occlusive disease of the great vessels due to arteritis, as seen predominantly in young women, from examples of subclavian-carotid obstruction of other causes.

Four relatively brief reviews of the subject of "pulseless disease" have appeared by Scandinavian, 9, 10 British 11 and Latin American 12 authors in the last three years. Seemingly because of the language problem, no literature-wide review has been achieved, and this report does not claim to be of this nature. The most comprehensive review yet to appear is that of Ross and McKusick in 1953. As previously mentioned, it dealt with unilateral and single vessel occlusions as well as with the more restricted condition discussed here.

INCIDENCE

Recent reports testify to the rarity of the bilateral subclavian-carotid obstruction syndrome. A 1954 review 9 disclosed only 28 reported cases exclusive of

TABLE 2

Clinical Manifestations of Chronic Subclavian-Carotid Obstruction

Clinical Manifestations

- I. Cardiovascular
- A. Absent carotid and radial pulsations
 B. Very-low-to-absent pulse pressure in arms
- C. Hypertension in legs
- D. Collateral circulation
- E. Cerebral arterial insufficiency
- F. Hypertensive heart disease
- G. Angina pectoris
- II. Head and neck
- A. Eye changes
 1. Transitory or progressive blindness
 2. Atrophy of iris

 - B. Arterial insufficiency 1. Claudication of jaw muscles
 - 2. Perforation of nasal septum

III. Increased erythrocyte sedimentation rate (Japanese cases)

Japanese reports. A review in 1952 8 included 58 cases from Japan and added one from this country with features similar to the Japanese cases. Thus, when discussion is restricted to bilateral absence of pulses in neck and arms, apparently less than 100 cases have been recorded.

CLINICAL PICTURE

The clinical manifestations have been categorized in various ways by a variety of authors. We have modified the classifications of others to include only two broad categories of clinical features (table 2).

No pulsation of carotid, brachial or radial arteries can be felt in the advanced case, although a faint expansion may be felt before the condition is advanced. In some case reports it has been mentioned that the arteries could be palpated easily as distended but not pulsating. If blood pressure can be determined at all with

^{*} Most common manifestations.

the cuff type of sphygmomanometer, it will be found that pulse pressure is greatly lessened, though mean arterial pressure is likely to be normal. In our own patient the cuff-measured pressure was 120/110 mm. of Hg six years ago, but it is now not measurable except by the flush technic.¹³ A few patients have experienced color or temperature changes in the hands, but trophic skin changes have been rare. Clubbing and cyanosis have been reported once.¹⁴ Fatigue, pain or "claudication" in the arms has been reported in several patients, ours included.

Hypertension in the lower extremities is the rule. Fifteen of 24 in whose reports blood pressure was recorded 5 showed a systolic pressure greater than 160 mm. Hg. It is considered a cardinal feature of the "young female arteritis" variety of the syndrome. This must be interpreted, however, in the light of the fact that much less is known concerning normal blood pressure in the lower extremity than in the upper. As a matter of fact, one study 15 has shown that in 25% of normal individuals the systolic pressure was between 170 and 195 mm. Hg. Our patient had distinctly elevated pressure in the legs by any standard.

Prominent collateral arterial circulation has been clinically obvious in many of the reported cases. This has been most often manifested as a bruit, either systolic or continuous, heard best at the base of the neck superior to either of the sternoclavicular joints. Less frequent evidences of dilated and tortuous arterial collaterals have been the presence of prominently dilated vessels over the back of the chest and rib erosion. Our patient showed both of these signs.

Arterial insufficiency in the brain has shown itself in several ways. Attacks of syncope have been in the history of a high percentage of patients. Vertigo has occurred in a large majority. Susceptibility to these two symptoms has been increased in most patients by standing or exercise. Several patients have shown exaggerated carotid sinus sensitivity. Convulsive seizures of a jacksonian or grand mal type have occurred also in several patients. Of 40 cases covered in one review, 13 had hemiparesis or hemiplegia. Those authors consider the cerebral manifestations of the condition under discussion to differ in no way from those of internal carotid thrombosis.

Several patients have had cardiac enlargement and failure. Hypertension, coronary sclerosis and, rarely, luetic aortic insufficiency have been the etiologic factors. Angina pectoris has been less common.

Regarding the category of clinical findings titled "head and neck," it is of course still the cardiovascular defect which is responsible, the findings being categorized separately only for anatomic separation. Inadequacy of cerebral circulation has been discussed. Other structures of the head and neck suffer, probably also from circulatory inadequacy. The eyes have shown a variety of symptoms and signs. More common symptoms are transient episodes of dimness of vision or blindness, plus progressive and permanent dimness or blindness later. Cataracts most often account for the progressive loss of vision. It is interesting that a few patients have experienced dim vision coming with exercise, a symptom which has been called "visual claudication." Fairly common causes of visual impairment have been retinal pigmentation and atrophy, atrophy of the iris, and corneal densities. Optic nerve atrophy has also been noted in several. In the Japanese cases it has been common to note peripapillary arteriovenous anastomoses. Several patients have been described as having visibly sluggish blood

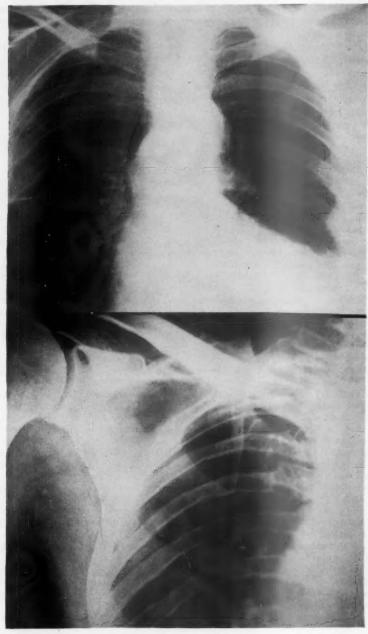


Fig. 1. Teleroentgenogram and special film to show rib notching. Note also cardiomegaly, pleural effusion, and calcification in ascending aorta.

flow in retinal vessels. A wreath of anastomotic arteries about the ocular papillae has been seen in a large majority of the Japanese patients in whom that examination was reported.

Other structures of the head and neck are less markedly and less frequently involved. Nasal septum perforation, collapse of nasal bridge, trophic facial skin changes, and claudication of masseter muscles have been occasional findings.

Falling in neither category is the laboratory finding of rapid erythrocyte sedimentation. Japanese, and other reports of the "young female" type of the disease, have emphasized that feature. Presumably it is on the basis of the arteritis producing the syndrome.

CASE REPORT

A 58 year old Negro male was admitted to the medical service of the John Gaston Hospital on March 19, 1949, because of exertional and nocturnal dyspnea and swelling of the ankles which had begun three months previously. There was a history of occasional exertional chest pains, relieved by rest.

He gave a past history of syphilis treated 10 or 12 years previously. The duration and kind of treatment were not known. There was a previous admission to the John Gaston Hospital in 1946 because of contusions of the chest and head. X-ray of the chest at that time showed old rib fractures but no evidence of recent injury.

The blood pressure was 106/96 mm. of Hg in the right arm and 110/100 mm. of Hg in the left. The radial pulses were barely palpable, and the pulse rate was 90. Expiratory wheezes were heard in the lungs bilaterally, and dullness was percussed in the left base. The heart was moderately enlarged to the left. As was accentuated. Systolic murmurs were present at the apex and base. In both scapular areas arteries of various lengths were felt to be prominent and tortuous. The longest segments measured 10 cm. Palpation of the intercostal arteries revealed pulsations greater than normal. The carotid artery pulsations were extremely weak, as were the radial and brachial. The femoral and dorsalis pedis pulsations were normal. The liver was tender and palpable 4 cm. beneath the right costal margin. There was moderate edema of the lower extremities.

The blood pressure was not obtainable in the upper extremities on some attempts. Systolic blood pressure in the lower extremities was 220 to 240 mm. of Hg by palpation of dorsalis pedis during release of cuff pressure.

Routine laboratory studies were normal. A blood Kahn test was negative.

Chest films (figure 1) showed cardiac enlargement with left ventricular preponderance. The aorta was dilated and moderately tortuous, and there was calcification in the arch. The thoracic aorta was well visualized and showed no anomaly. There was notching of the inferior border of the ribs bilaterally, most marked in the upper ribs. Evidence of a small amount of pleural fluid in the left base was present on admission but later disappeared.

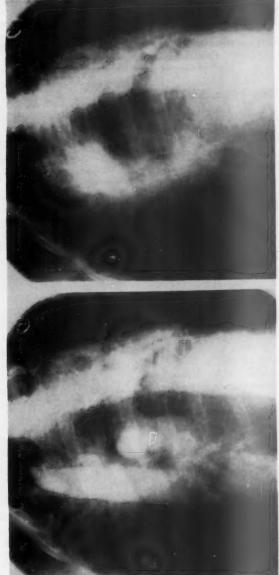
An angiocardiogram (figure 2) demonstrated the arch of the aorta clearly without constriction. The subclavian and carotid arteries did not fill. An electrocardiogram showed nonspecific abnormalities and digitalis effects.

With treatment the symptoms and signs of congestive heart failure disappeared,

and the patient was followed in the Out-Patient Department.

In February, 1951, he was admitted to the surgical service because of a laceration of the forehead and ankle and a transitory period of unconsciousness after having been struck by a streetcar. The physical signs were as before. There were no signs of congestive failure.

In January, 1953, he was seen in Neurology Clinic because of several "falling



Angiocardiogram. Film on left shows filling of vena cava, right ventricle and pulmonary artery. Film on right shows left ventricle and ascending aorta plus arch, but no great vessels branching. FIG. 2.

out" spells, probably convulsions, occurring during the preceding three weeks. Neurologic examination was negative. Skull films and an electroencephalogram were normal. Dilantin therapy was started.

In April, 1953, there was a hospital admission because of bacterial pneumonia in the right upper lobe. It slowly resolved with antibiotic therapy. During this admission calcification was noted in the ascending aorta on the chest film. The findings were considered diagnostic of syphilitic aortitis.

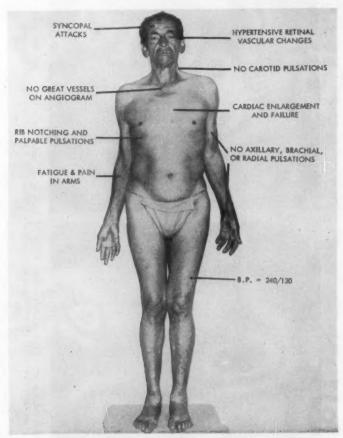


Fig. 3. A photograph of our patient illustrating a summary of clinical findings.

In 1954 and 1955 congestive failure was more prominent and required more frequent clinic visits, mercurial diuretics and occasional admissions to the hospital. The heart became larger. The electrocardiogram showed evidence of left ventricular hypertrophy and ventricular premature beats. On several observations the radial and carotid pulses were absent or barely perceptible.

On July 14, 1955, the blood pressures were recorded as right arm, 70/56 mm. of

Hg; left arm, 70/60 mm. of Hg; left leg, 280 systolic by palpation. The next day the blood pressure was not obtainable in the upper extremities, and was 180/70 mm. of Hg in the right leg. On several visits he complained of pain in both arms, sometimes severe, thought to be consequent to arterial insufficiency in the upper extremities. Priscoline was started and seemed to be beneficial.

The patient was last seen on October 20, 1955, at the age of 64 years, and was doing well except for exertional dyspnea. There were no physical signs of congestive failure. (See figure 3 for summary of clinical findings in this case.)

ETIOLOGY

Very few cases of bilateral chronic subclavian-carotid obstruction syndrome have been studied at autopsy; hence, little is certain about etiology. A review in 1954 12 disclosed only seven cases in which a complete autopsy had been done. One of these showed atheromatous occlusion of ostia, three had syphilitic aneurysm, and the remaining three showed "arteritis," "an inflammatory process of infectious character," and "a syndrome of panarteritis, probably syphilitic." In their 1952 review 11 of 18 cases which excluded Japanese reports, Skipper and Flint concluded that nine patients showed presumptive or certain evidence of syphilis, and that syphilis was probably excluded in the remainder. Two autopsied cases were shown to be due to atheroma. It is a satisfactory summary to state that the condition has various causes, among them arteriosclerosis and syphilis, but the most frequent cause seems to be an arteritis of unknown origin, which principally affects the supra-aortic trunks and appears most frequently in young women.12 It may be that Japan is geographically favorable for this arteritis of young women, though its prominence there may be merely a matter of awareness.

No record of an autopsied case with etiology other than syphilis, atheroma or arteritis of unknown cause was found. In at least two with aneurysm there was also a history of rather severe chest trauma preceding the development of symptoms. Several etiologic types are discussed by Ross and McKusick ⁵ with regard to aortic arch syndromes, and any of these could conceivably be responsible for the full bilateral occlusion picture. One of these was syphilitic aortitis without aneurysm, which seems likely as the etiology in the case which we are reporting. Development of local atheromatosis is favored by syphilitic aortitis, and this combination has been suggested as a cause in some cases. Healed dissecting aneurysm, ⁵ thrombophilia, ¹⁶ congenital anomalies ⁵ and extravascular mediastinal tumor ⁵ are possible causes which must be given consideration in any case. A more detailed discussion of etiology is presented in other reports. ^{5, 9}

TREATMENT

Penicillin treatment of aortic syphilis certainly should be carried out if that is the diagnosis. Until the cause of the obscure arteritis is determined, no progress is likely regarding treatment of the "arteritis of young women." It seems reasonable, however, that if the subclavian-carotid obstruction syndrome is diagnosed in a young woman, wherein the etiology may be presumed to be arteritis, adrenal cortical steroid therapy might be worth trying. Therapy for the syndrome due to other etiologies must await further advances in vascular surgery.

Symptomatic treatment of carotid sinus sensitivity with atropine-like drugs would be important if indicated.

SUMMARY

1. A review of the subject of "pulseless disease," better termed "chronic subclavian-carotid obstruction syndrome," has been presented. A case is reported in which syphilitic aortitis is considered to be the cause.

2. Chronic obstruction of the great vessels branching from the aortic arch results in syncopal attacks, eye symptoms and signs, absence of pulses in the neck and arms, and collateral arterial circulation as the most prominent clinical features.

This syndrome is most commonly due to arteritis of an obscure etiology. Syphilis and atheroma are less common causes.

SUMMARIO IN INTERLINGUA

In communicationes anglese, le termino "pulseless disease (morbo apulsatile)" ha essite le designation le plus popular pro un condition que esserea appellate plus accuratemente "syndrome de chronic obstruction subclavian-carotide." Le termino "revertite coarctation del aorta" ha etiam essite usate, proque il se disveloppa in iste condition un typo de circulation collateral que es vidite in coarctation del aorta. Le function de iste circulation es portar sanguine arterial verso le capite, le collo, e le extremitates superior plus tosto que verso le trunco e le extremitates inferior. Le majoritate del casos es reportate in le litteratura japonese (morbo de Takayasu). Le disordine es rar. Apparentemente minus que 100 casos del syndrome bilateral ha essite reportate. In le majoritate del casos japonese, arteritis a causa indeterminate constitueva le etiologia. Le majoritate del patientes esseva juvene feminas. Syphilis e atheroma ha essite plus rar como causas.

Le characteristicas clinic include un diminution o le absentia de pulsation carotide, brachial, e radial; restringite pression de pulso in le extremitates superior; fatiga, dolor, o "claudication" in le extremitates superior; hypertension in le extremitates inferior; prominente circulation collateral arterial, manifeste in un ruito proxime al articulation sterno-clavicular; palpabile allargamentos del arterias intercostal e periscapular; erosion costal; e insufficientia arterial del provision de sanguine al capite, manifeste in attaccos syncopic, vertigine, vision defective, cataractas, claudication del musculo masseter, e altere effectos.

Es reportate le caso de un 58-enne masculo negre con iste syndrome. Le patiente se presentava originalmente con signos de insufficientia cardiac. Le historia antecedente includeva syphilis 10 a 12 annos previemente. Le pression de sanguine del extremitates superior esseva 110/100 mm Hg. Le extremitates inferior habeva hypertension. Le corde esseva allargate. Le pulsation carotide, brachial, e radial esseva absente. Un test sanguinee de Kahn esseva negative. Roentgenogrammas thoracic revelava indentation bilateral del margine inferior del costas. Un angiocardiogramma revelava nulle grande vasos exiente ab le arco aortic. Le etiologia pareva esser aortitis syphilitic o arteritis syphilitic del grande vasos. In le curso de septe annos de observation consecutori le patiente habeva un breve periodo de disconforto e excessos de fatiga post effortio in le extremitates superior. Ille etiam experientiava attaccos convulsive durante un breve periodo. Therapia a Dilantina resultava in lor cessation. Le patiente se trova ben sub therapia pro insufficientia cardiac.

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HYPERLIPEMIA ASSOCIATED WITH DIABETES MELLITUS AND PANCREATITIS: A CASE REPORT WITH AUTOPSY*

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INTEREST in the relationship between diabetes mellitus, hyperlipemia and pancreatitis was stimulated early by sporadic reports of lactescent serum found incidentally in cases of diabetes mellitus and pancreatitis. This interest has been increasing in the last few years with the appearance of many articles with de-

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tailed serum lipid partitions which shed further light on this subject. The problem is to determine what etiologic relationship exists between these conditions.

Brunner,¹ Gardner,² Edmondson ⁸ and others ^{4, 5, 6} have shown that hyperlipemia occurs in acute and in chronic relapsing pancreatitis. It was suggested by Kennedy and Collett ⁷ and by Klatskin and Gordon ⁸ that the hyperlipemia might be responsible for the chronic relapsing pancreatitis by the mechanism of fat embolism. Unfortunately, there is little pathologic material available upon which to base the conclusions drawn from physiologic data.

The following is a case report in which the combination of extreme hypercholesterolemia and hyperlipemia with diabetes mellitus and acute pancreatitis failed to reveal any evidence of fat emboli at autopsy. It is believed that the hyperlipemia may represent the type associated with "essential hyperlipemia."

CASE REPORT

A 47 year old white man entered the hospital for the first time on September 25, 1954 because of four months' history of paresthesias, polydipsia, polyuria, polyphagia, nocturia, weakness and malaise, and a 35 pound weight loss. He denied having chills or fever, nausea, vomiting or diarrhea. He had no knowledge of having tuberculosis, venereal diseases or diabetes mellitus. There was no family history of diabetes, skin eruptions or significant gastrointestinal disorders. The patient was reported by his mother to drink excessively.

When examined he was found to be malnourished and to have an alcoholic odor on his breath. Pulse was 116 and regular; blood pressure, 120/70 mm. of Hg. The presence of lipemia retinalis was not recorded. Hepatosplenomegaly was not detected. The serum was chylous on entry and until discharge. Chest x-ray was normal, and the Wassermann test was negative. Blood count: hemoglobin, 16.5 gm.; white blood cells, 7,800. Urine: 2 plus sugar, 4 plus acetone. Blood chemistries: sugar, 324 mg. %; carbon dioxide combining power, 18 mEq./L.; nonprotein nitrogen, 27 mg. %; albumin, 4.3 gm. %; globulin, 1.6 gm. %; calcium, 5.0 mEq./L.

The patient was placed on a diet of 300 gm. of carbohydrate, 90 gm. of protein and 90 gm. of fat and was given insulin. Urinary acetone disappeared in two days, and urine sugar decreased to a trace in five days. He was taking 45 units of NPH insulin when discharged on October 6, 1954.

Following discharge the patient apparently returned to his previous alcoholic excesses and did not return to clinic. He took insulin irregularly and his supply ran out 10 days prior to the last entry. He rapidly became weak, developed a cough and was unable to walk. Abdominal pain began the day before admission and the patient

was described as being lethargic that night.

He was re-admitted the following day, December 11, 1954, at 10:25 a.m., dirty, restless, stuporous and dehydrated, and breathing with Kussmaul's respiration. Pulse was 120 and regular; blood pressure, 110/60 mm. of Hg. Lipemia retinalis was noted for the first time and remained until death. The abdomen was firm and slightly tender. Hepatosplenomegaly was not detected, and pedal pulses were not palpable. Neurologic examination was grossly normal except for the depressed sensorium. The skin contained no xanthomata.

Admission laboratory work was as follows: hemoglobin, 11.0 gm.; white blood cells, 14,900; packed cell volume, 42%; urine, pH 5.0; urinary albumin, 1 plus; sugar, 4 plus; acetone, 4 plus; blood sugar, 681 mg. %; carbon dioxide combining power, less than 5 mEq./L.; serum ketones, 167 mg. % (normal, less than 5 mg. %); serum amylase, reported only as "moderate activity, unable to read accurately because of extremely chylous serum." Heparin was added to the serum in equal parts and pro-

duced no grossly detectable change. The remainder of the electrolytes and subsequent chemistries may be seen in table 1.

Treatment with insulin and fluids was started immediately. A total of 950 units of crystalline zinc insulin, 5,800 c.c. of fluid and 21 gm. of KCl was given in the first 24 hours. The patient was awake in less than three hours. At the second hour the blood pressure dropped to 80/? mm. of Hg, and norepinephrine was given to maintain normal levels until the twentieth hour. Urine output remained adequate throughout. Urine sugar and acetone decreased to 1 plus and negative, respectively, by the twenty-sixth hour, and remained at those levels until death. The packed cell volume dropped to 32% after 24 hours despite 500 c.c. of whole blood. The carbon dioxide combining power rose to 17 mEq./L. in nine hours and to 21 mEq./L. in 20 hours. The lowest serum potassium was recorded four hours after entry, shortly after parenteral KCl therapy was started. Repeated electrocardiograms revealed only low left ventricular T waves, attributable to mild hypokalemia. Penicillin was given from admission, 600,000 units twice daily. A fever of 101° F. rectally was noted on the second day, at which time tetracycline, 100 mg. every eight hours intramuscularly, was substituted. Fever continued, up to 102° F. orally, until death. A serum amylase deter-

TABLE 1

Day	Hour	Sugar mg.%	CO ₂ mEq.	NPN mg.%	C1 mEq.	PO ₄ mEq.	Ca mEq.	Mg mEq.	Na mEq.	K mEq.	Ket- ones	PCV	Urine	
													Sugar	Acet
Normal		80- 110	26- 33	25- 39	98- 108	2-3	4.5- 5.5	1.1-2.2	130- 145	4.1- 5.6	<5 mg.%	45	0	0
12/11	11 a.m. 1 p.m. 2 p.m.	681 504 394	<5 <5		89 95	4.46 1.65	3.6 3.5	1.96 1.35	111 115	4.2 3.6 3.34 2.7	167	42	4+ 3+ 3+ 3+	4+ 3+ 3+ 3+
	3 p.m. 5 p.m. 8 p.m. 11 p.m.	324 396	17	37	92 101 105	0.45 0.35 0.31	3.8 3.7 3.5	1.22 1.22 1.16	115 122 126	2.98 3.23 3.08	155 96 51		3+ 3+ 4+	4+
12/12	7 a.m. 11 a.m.	230 128	20		115	1.07	4.0	1,12	130	4.1	12	32	3+2+	tr tr 0
12/13	8:30 a.m.	59	21	43						4.3			1+	0

mination done on December 13 was read as "approximately 300 Somogyi units." No organisms were cultured from blood drawn on December 13. On December 14 the patient was noted to be weak, febrile, anorexic and slightly nauseated. Respirations were 25 and pulse was 96. The lungs were clear. The abdomen was 1 to 2 plus tender in the right hypochondrium. The liver was not enlarged and the bowel sounds were normal. Chest x-ray taken at this time was normal, and abdominal x-ray was reported only as "moderate ileus." On return to the ward the patient was shaky and refused food, and died suddenly at 12:30 p.m., December 14, 1954, 74 hours after entry.

At autopsy the body was moderately emaciated. The central nervous system was grossly normal. The heart weighed 350 gm. Moderate atherosclerosis of the coronary arteries without significant luminal encroachment was noted. The aorta contained a "moderate amount of intimal lipoid plaques." The lungs were edematous; the lobes were firm, rubbery and congested. The pulmonary arteries revealed no gross evidence of embolism.

The peritoneal cavity contained 500 to 700 c.c. of yellowish milky fluid, mostly in the lesser sac. Submucosal petechiae were noted in the stomach. The pancreas was swollen and firm, and fat necrosis was evident, especially on its ventral surface. The lobular architecture, however, appeared intact. The pancreatic duct contained

some inspissated material, but no calculi were found. Areas of fat necrosis immediately surrounding the main pancreatic duct were present. A common channel for the biliary and pancreatic ducts existed for only about 1 mm. No fat necrosis was evident elsewhere.

The liver weighed 2,850 gm. and was irregularly mottled with some central venous congestion. No calculi or inflammation was noted in the gall-bladder. The spleen weighed 120 gm. and did not appear abnormal. The kidneys were slightly pale but otherwise appeared normal. The pituitary, thyroid and adrenal glands were not abnormal.

The microscopic sections were reviewed in detail by Dr. Hugh Edmondson. Fat stains (both Scharlach R and osmic acid) of the pancreas, lungs, heart, liver and kidneys were examined for fat deposition and emboli. There were congestion and edema of the lungs. Some of the medium sized pulmonary vessels contained stainable lipid, not considered significant pathologically. An occasional capillary was likewise involved. The pancreatic acinar cells showed fatty changes similar to those so often associated with fatty livers from any cause. Recent peripheral and septal fat necrosis was prominent, but again the acini were largely preserved. Some of the veins contained an amorphous material which partially stained for fat. No evidence of arterial or capillary fat embolus was found. Occasional hepatic arteries contained some lipid. Fatty changes were present in about one third of the hepatic cells, with occasional large fat droplets, but no definite fat emboli were seen. The spleen, thyroid, adrenals and pituitary had no significant changes. The kidneys showed minimal congestion but none of the changes of diabetic nephropathy.

Paper chromatographic studies of the serum with stains for protein and lipid were made. The beta-2 globulin was extremely high and saturated with fat. The gamma globulin was low.

DISCUSSION

The duration of diabetes in our patient is unknown. The hyperlipemia was discovered on his first entry coincident with mildly uncontrolled diabetes mellitus. The hyperlipemia and lipemia retinalis were found on his second entry coincident with diabetic coma. The clinically suspected pancreatitis was confirmed at autopsy. Treatment with insulin, fluids and electrolytes produced a rapid and satisfactory clinical response, with the blood sugar, carbon dioxide combining power and serum ketones approaching normal at the end of 24 hours. The serum phosphate fell markedly during treatment, but the lowest potassium level was 2.7 mEq./L. and returned to normal shortly thereafter. The nonprotein nitrogen was not significantly elevated. The fall in total serum lipids 2nd in neutral fat was no greater than would have been expected from hydration alone. Fully adequate anatomic cause for death was not found at autopsy. In addition, and importantly so, fat stains (osmic acid and Scharlach R) of the lungs, pancreas, liver, kidney and heart, or hematoxylin and eosin stains of other organs (aorta, spleen and brain), did not reveal fat embolism.

It has long been recognized that hyperlipemia often accompanies severe untreated diabetes mellitus.^{9, 10} In fact, all of the extreme total serum lipid values were found in such cases.^{4, 6, 11, 12} Serum lipid fractions in these cases have shown the greatest disturbance to be an elevation of neutral fat. Cholesterol values greater than 1,596 mg. % (reported by Marble and Smith ¹¹) were not discovered in a review of the literature ^{8, 12, 18, 14, 15} although in many cases with extreme hypercholesteremia, lipid partitions were not reported. Thannhauser ¹³ and Joslin ¹⁶ both state that the hyperlipemia of severe untreated diabetes re-

sponds rapidly to treatment, and others 6, 11, 17 have produced precipitous drops in total serum lipids in 24 hours or less.

The lipid partition in essential hyperlipemia is similar to that in severe untreated diabetes, except for the slightly higher cholesterol values in the latter. The neutral fat values are again the most elevated. Hypercholesteremic states are also known to be present in myxedema, Rephrosis Rephro

TABLE 2

	12/1	11/54	12/	12/54	Normal		
	Mg.%	% of Tot.	Mg.%	% of Tot.	Mg.%	% of Tot	
Total cholesterol Phospholipids Neutral fat Total serum lipids	4,200 1,280 4,700 12,500	33.6 10.2 56.2 100.0	3,200 875 1,385 7,000	45.7 12.5 41.8 100.0	264 219 130 636	43 36 21 100	

The serum lipid determinations were done by the Bio-Science Laboratories of Beverly Hills, California, under the direction of Dr. Richard J. Henry. The methods used may be found in the following references:

Phospholipids.

Youngburg, G. E., and Youngburg, M. V.: Phosphorus metabolism. I. A system of blood phosphorus analysis, J. Lab. and Clin. Med. 16: 158, 1930.

Total cholesterol:

Bloor, W. R.: The determination of cholesterol in blood, J. Biol. Chem. 24: 227, 1916.

Cholesterol esters:

Bloor, W. R., and Knudson, A. J.: The separate determination of cholesterol and cholesterol esters in small amounts of blood, J. Biol. Chem. 27: 107, 1916.

Total serum lipids:

Wilson, W. R., and Hanner, J. P.: Changes of total lipid and iodine number of blood fat in alimentary lipemia, J. Biol. Chem. 106: 323, 1934.

Neutral fat = Total fat -(free cholesterol + 1.67 × cholesterol esters + phospholipids).

Normal values

Ahrens, E. H.: The lipid disturbance in biliary obstruction and its relationship to the genesis of arteriosclerosis, Bull. New York Acad. Med. 26: 151, 1950.

parison, table 2 contains the serum lipid partition of this patient on admission and again 24 hours later. It may be seen, first, that the fall in total serum lipids and in neutral fat in this patient did not significantly exceed that which would be expected from hydration alone; second, that the lipid values correlate closely with those of essential hyperlipemia and diabetes mellitus except for the extreme elevation of total cholesterol; and third, that the lipid values plus clinical and pathologic findings do not correlate with other hypercholesteremic states.

Many authors have reported abdominal crises associated with hyperlipemia. 14, 15, 28 Several of these—namely, Wijnhausen (as quoted by Thannhauser 18), Root, 4 Poulsen 5 and Edmondson 8—have presented anatomic evidence, either by autopsy or laparotomy, that pancreatitis was present. Yet none recorded fat embolism in the pancreas itself. Gardner ² and Klatskin and Gordon ⁸ report serum amylase values indicative of acute pancreatitis. In attempting to establish an etiologic relationship between hyperlipemia and pancreatitis, Klatskin and Gordon ⁸ suggested that the pancreatitis was due to fat embolism, admittedly on circumstantial but nevertheless highly convincing evidence. Although we were unable to confirm this theory, we were also unable to demonstrate any other etiology for the acute pancreatitis. From the clinical evidence, it is not believed that the pancreatitis antedated the onset of the hyperlipemia or even the diabetic acidosis.

A case of persistent hyperlipemia associated with diabetes mellitus was recently reported by Haymond and Berry.²⁴ Evidence for essential hyperlipemia was the persistence of the hyperlipemia despite adequate control of the diabetes, and response to a low fat diet. The question arises as to whether the present case represents essential hyperlipemia and diabetes or hyperlipemia due to severe untreated diabetes. Several facts indicate that this might be essential hyperlipemia: lactescent serum at a time when only mild ketosis was present; total serum lipids that did not fall significantly with adequate therapy of the diabetes; and the absence of hepatosplenomegaly, which Thannhauser ¹³ states is rarely absent in the adult patient with this disorder. Despite these facts, it cannot be stated with certainty that this represents essential hyperlipemia. The extreme hypercholesteremia has not yet been reported in either entity.

Concerning the zone electrophoretic pattern of the serum in this case, several workers have made chromatographic studies after heavy fat meals and in various types of lipemia. 25, 26, 27 It has been noted that the beta globulin normally contains most of the lipid and three fourths of the total cholesterol. The beta-2 fraction consists of nonmigrating lipoproteins between the beta and gamma fractions, is richest in neutral fat, and probably contains giant lipoprotein molecules and chylomicra. In essential hyperlipemia, as well as in diabetes mellitus, the beta lipoprotein fraction contains considerably more cholesterol and especially neutral fat. In essential hyperlipemia, however, the neutral fat peak occurs closer to the beta-2 globulin. Our case demonstrates a similar pattern in that the beta-2 globulin fraction was extremely high and contained large amounts of material stainable as lipid.

SUMMARY

A case is reported of extreme hypercholesteremia, hyperlipemia, diabetes mellitus and acute pancreatitis, in which no evidence of fat embolism as a cause of pancreatitis was found at autopsy. Lipid analyses and paper chromatographic studies of the serum are included. The cholesterol value of 4,200 mg. % is believed to be the highest reported in any case of diabetes mellitus, essential hyperlipemia or pancreatitis.

ACKNOWLEDGMENTS

We are deeply indebted to Dr. Helen E. Martin, Professor of Medicine, and to Dr. Hugh A. Edmondson, Professor of Pathology, University of Southern California School of Medicine, for clinical assistance and interpretation of pathologic material.

SUMMARIO IN INTERLINGUA

Le co-occurrentia de hyperlipemia e acute pancreatitis con diabete mellite in un unic caso necropsiate es presentate con le objectivo de tentar monstrar un relation inter iste conditiones. Un masculo blanc de 47 annos de etate con hyperlipemia a

un tempore quando su diabete esseva sub controlo e con total lipidos seral que non descendeva con rapide subjugation de coma diabetic moriva subitemente le quarte die de su hospitalisation. Le kalium seral esseva normal le die ante le morte, e nulle acetonuria esseva presente. Le valores del amylase seral esseva moderatemente augmentate, sed accurate lecturas non esseva possibile a causa del presentia de un sero de comportamento de crema. Le examine necroptic revelava solmente acute pancreatitis con necrosis de grassia, edema pulmonar, e minime alterationes de grassia in le hepate. Special colorantes de grassia applicate al pancreas, pulmones, hepate, e ren non revelava ulle embolos de grassia. Nulle adequate causa del morte esseva trovate.

Le partition de lipido revelava un marcate augmento del total lipidos seral, del grassia neutre, e specialmente del cholesterol seral, con un valor maximal de 4.200 mg% pro iste ultime. Un revista del litteratura produceva nulle reporto de un valor plus alte que le presente, tanto in hyperlipemia essential como etiam in non-subjugate diabete mellite. Studios de chromatographia a papiro monstrava in le sero un altissime nivello de globulina beta-2 saturate con grassia. Ambe le mentionate phenomenos es documentate pro hyperlipemia essential e non-subjugate diabete mellite.

Super le base del datos presentate, nos suggere que in iste caso le hyperlipemia representa le hyperlipemia que es causate per hyperlipemia essential, que illo precedeva le declaration de clinic diabete mellite e certo le acute pancreatitis, e que—ben que illo es possibilemente connectite in un o un altere maniera con le pancreatitis acute—le opinion de altere autores que embolismo pancreatic de grassia pote resultar in acute necrosis pancreatic non esseva corroborate. Le presentia del extreme augmento de cholesterol seral remane inexplicate.

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FATAL RUPTURE OF A TUBERCULOUS AORTIC ANEURYSM: A CASE REPORT*

By James L. German, M.D., and Charles L. Green, M.D., McKinney, Texas

DIFFICULTY in diagnosis as well as in treatment is to be expected in cases such as the following, which is reported as a rare complication of tuberculosis. In a case of aneurysm of the aorta of obscure etiology it is to be recalled that a tuberculous process may involve that vessel.

CASE REPORT

A 36 year old Negro man entered the Surgical Service of the Veterans Hospital, McKinney, Texas, in moderate distress from abdominal pain but not apparently an "emergency." He died suddenly 18 hours after admission. One month prior to admission he had experienced the sudden onset of epigastric pain which penetrated to the back; it became progressively more severe up to the time of hospitalization. This pain was aggravated by body motion and also by food intake. He recently had lost 14 kg., even though his appetite had remained good. Over the same period of time he had noted constipation and a progressively enlarging "lump" in the abdomen. This "lump" appeared at about the time of onset of the symptoms. There was one episode during which a small amount of bright red blood was passed by rectum.

* Received for publication June 27, 1955.

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There was a past history of high blood pressure 18 months prior to admission, at which time he had been "bedridden" for vague reasons. He stated that he had had syphilis in 1944 while in the Army. Official records of the Surgeon General's department revealed that he had had negative serologic tests for syphilis in 1940 and in 1942; in 1944 he had gonorrhea and primary syphilis, manifested by a penile lesion and a positive Kahn test. He received adequate penicillin therapy at that time, in accordance with the Army regulation for treating syphilis. Subsequently (in 1944) cerebrospinal fluid examination was negative for syphilis, and in 1945 and 1946 blood serologic tests for syphilis were negative. No other significant past history was obtained.

Positive physical findings on hospital admission included evidence of recent weight loss. He was seemingly in good general condition except for pain. Temperature was 100° F. There was a firm, moderately tender, fixed epigastric mass with expansile pulsations. Pupils were not abnormal.

Laboratory studies showed a hemoglobin of 10.3 gm., a white blood cell count of 8,000, with 73% neutrophils and 27% lymphocytes, no urinary abnormalities, negative serum Wassermann and Kahn tests, and negative agglutination tests for brucellosis and tularemia.

Treatment included analgesics, mild sedation, and gastric suction through a Levin tube. The patient appeared somewhat confused and restless 15 hours after admission, moaning with pain. Eighteen hours after admission he was found moribund — cold and clammy, with gasping breath, barely audible heart sounds, and undetectable blood pressure — and died shortly afterwards.

Autopsy was performed 24 hours after death. In the right anterolateral wall of the abdominal aorta, 1 cm. below the renal arteries, was a 4 by 3.5 by 5 cm. saccular aneurysm. From the posterolateral border of the aneurysm a 3 by 1.5 cm. outpouching extended into the psoas muscle. The wall of the aneurysm was dense fibrous tissue 0.5 cm. thick. The intimal surface was thrown into folds, covered by recent blood clot and an adherent organized thrombus. There was a 1.5 cm. rupture in the right lateral wall of the aneurysm, and there were 2,500 ml. of blood behind the peritoneum extending from the diaphragm to the sacrum and laterally to the psoas muscles. Firm, matted lymph nodes surrounded and were adherent to the aneurysm and to the colon. Sectioned surfaces of the nodes showed yellow-green areas of

Other pertinent autopsy findings were encapsulated calcific and caseous nodules in the apex of the left lung and left hilar lymph nodes; non-encapsulated 0.5 to 1.5 cm. caseous nodules in the spleen and liver; and a firm white 0.5 by 0.5 by 1 cm. nodule in the left epididymis.

There was no evidence of syphilis, such as extensive atherosclerosis, intimal scarring or focal adventitial fibrosis. No penile scars were found. The blood passed from the rectum was explained by hemorrhoids.

The lesions involving the lymph nodes, liver, spleen and epididymis were circumscribed but non-encapsulated granulomata showing central necrosis, partially caseation necrosis, peripheral epithelioid cells and Langhans' giant cells, and surrounding fibrous tissue and chronic inflammatory reaction. Acid-fast organisms were demonstrated by Campbell's modification of Ziehl-Neelsen's stain, and Mycobacterium tuberculosis was cultured and removed from guinea pigs inoculated with suspensions of tissue from the liver and aortic lymph nodes.

The wall of the aorta adjacent to the adherent lymph nodes was partially replaced by dense fibrous tissue in which were diffusely arranged lymphocytes. The adventitia of the aorta, capsules of lymph nodes, and intervening tissue were inseparable and replaced by fibrous tissue in which were rare granulomata. Rare necrotic areas were present in the adventitia. No perivascular medial scarring, perivascular lymphocytic infiltration, endothelial proliferation or focal adventitial fibrosis suggestive of syphilis

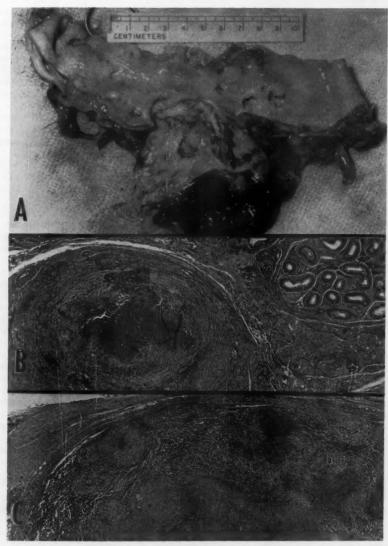


Fig. 1. A: Abdominal aorta and ruptured aneurysm. B: Tuberculosis of the epididymis, showing poor encapsulation and central necrosis, in part caseation necrosis. H. and E. stain. $16\times$. C: Tuberculosis, para-aortic lymph node, with involvement of lymph node capsule and extension to perinodal tissue and adjacent wall of aortic aneurysm. H. and E. stain. $34\times$.

was found. The wall of the aneurysm was dense fibrous tissue in which were dif-

fusely arranged lymphocytes and rare granulomata.

Pathologic Diagnoses: (1) Tuberculosis, apex left lung, liver, spleen, left epididymis, and lymph nodes (hilar, mediastinal, and para-aortic). (2) Aneurysm, abdominal aorta, due to extension of tuberculosis from para-aortic lymph nodes; rupture of aneurysm with retroperitoneal hemorrhage. (3) Calcification of hilar lymph nodes.

DISCUSSION

A mycotic aneurysm of the abdominal aorta resulting from tuberculous lymph nodes being in juxtaposition with the aorta, or from tuberculous aortitis, is an unusually rare condition. A review by Scott, Maxwell and Grimes in 1949 b disclosed a total of 23 such cases, including their own case, and there have been few reported since. The aneurysm is the result of erosion-necrosis of the aortic coats by neighboring tuberculous nodes. Occasionally the aneurysm results from invasion and weakening of the aortic wall itself by hematogenous tuberculosis in the absence of neighboring nodes. The sac, or occasionally only a sinus tract, eventually ruptures into peritoneal or retroperitoneal spaces. If adhesions attach the mass to a hollow viscus (e.g., jejunum, duodenum or stomach), rupture may occur into the viscus, producing hematemesis and melena.

The case reported here was a young Negro who had had fever, weight loss, abdominal pain and abdominal tumor for a month, these symptoms increasing until he died suddenly from retroperitoneal rupture of an aortic aneurysm which had formed in a tuberculous para-aortic lymph node mass. The pathogenesis of the aneurysm is considered to be hematogeneous dissemination of tuberculosis from the lung and lymphatic spread from the epididymis to para-aortic lymph nodes. Extension of the disease from lymph nodes to adjacent aortic wall with replacement of elastica and media resulted in an aneurysm which ruptured. Since adherence of the aneurysm to the sigmoid colon with mucosal change had begun, rupture into that viscus was a potentiality.

SUMMARY

An unusual case of false aneurysm of the abdominal aorta is reported, the aneurysm having formed in a closely adherent tuberculous para-aortic lymph node mass. Rupture with retroperitoneal exsanguination produced death. Tuberculosis was present also in the lung (inactive), liver, spleen, epididymis and hilar-mediastinal lymph nodes. The clinical picture, which was undiagnosed, included abdominal pain, expansile abdominal tumor, fever and weight loss.

This is an unusual complication of "tabes mesenterica," itself infrequent today along with the generally decreasing incidence of tuberculous lymphadenitis.

SUMMARIO IN INTERLINGUA

Es presentate un caso inusual de aneurysma del aorta abdominal, secundari a adenitis tuberculotic. Le patiente, un masculo negre de 36 annos de etate, se plangeva de sever, penetrante dolores epigastric de un mense de duration, de un tumor abdominal, e de perdita de peso. Le examine physic al tempore del admission al hospital revelava leve grados de emaciation, basse grados de febre, e un fixe sed expansile massa epigastric que esseva firme e sensibile sub pression. Le patiente moriva inexpectatemente 18 horas post su admission. Nulle diagnose esseva establite ante morte.

Le necropsia revelava un ruptura de un saccular aneurysma del aorta. Le mesuras del aneurysma esseva 4 per 3,5 per 5 cm. Illo prendeva su origine anterolateralmente, immediatemente infra le arterias renal. In iste area le adventitia, le firme nodos lymphatic adjacente, e le histos inter illos formava un inseparabile massa in que le aneurysma se habeva disveloppate. Le nodos e le pariete del aneurysma exhibiva le typic aspectos pathologic de tuberculose. Organismos acido-resistente esseva trovate per frottis e inoculation in porcos de India. Active lesiones tuberculotic esseva etiam trovate in hepate, splen, epididymis, e thoracic nodos lymphatic. Ancian tuberculose caseose esseva trovate in le apice pulmonar. Le caso non presentava datos in supporto de un etiologia syphilitic. Le aneurysma se habeva rumpite con un resultante massive hemorrhagia retroperitoneal como causa immediate del morte.

Le revista del litteratura revela que in iste rarissime condition, le ruptura pote facer se a in le vias gastrointestinal o le cavitate peritoneal e etiam a in le spatio retroperitoneal. In aneurysmas aortic de etiologia obscur, le possibilitate de tuberculose debe esser prendite in consideration.

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FRUCTOSURIA: REPORT OF A CASE *

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ALL melituria is not glucosuria. This perfectly sound statement seems acceptable to all. But the fact is easily forgotten. Melituria associated with glycemia exceeding the accepted range of normal is naturally assumed to be true glucosuria. And in time one's thinking may become so tracked clinically as to assume that melituria exhibited simultaneously with a normal glucose tolerance is likewise simple glucosuria, perhaps of the "low threshold" type. Such was the impression after four loading tests in the instance cited below. A family history of diabetes seemed to confirm this deduction.

^{*} Received for publication December 21, 1955.

From the U. S. Army Hospital, Wurzburg, Germany, March, 1954. Requests for reprints should be addressed to Alfred R. Lenzner, M.D., 685 Delaware Avenue, Buffalo 9, N. Y.

CASE REPORT

A 20 year old soldier entered the U. S. Army Hospital at Wurzburg, Germany, in March, 1954, with the chief complaint of recurrent dizziness. He believed this to be causally related to diabetes, diagnosed on the basis of repeated positive Benedict's tests in urinalyses.

In the family history a maternal grandmother had died at the age of 70 with diabetes requiring insulin for control. There were four siblings, all without known diabetes. One brother, always over 255 pounds, had been large at birth. The patient's mother had been diabetic for six years and had had one episode of diabetic

ORAL FRUCTOSE TOLERANCE

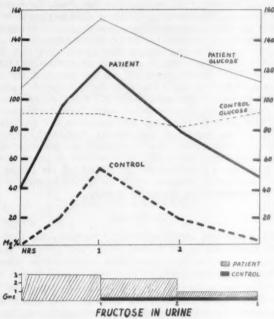


Fig. 1. Oral fructose tolerance test.

coma marked by a blood glucose of 575 mg, per 100 ml. Her current daily insulin requirement was 60 units.

The patient's pertinent diabetic history prior to military service included rejection for industrial employment in November, 1953, on the basis of a positive urinalysis. The family physician had then found his fasting blood glucose to be "less than 150." In January, 1954, two months after the start of his European tour of duty, study at the U. S. Army Hospital at Frankfurt, Germany, had included two oral and two intravenous glucose tolerance tests. The highest glucose level attained throughout was 137 mg. per 100 ml. The majority of the concomitant samples of urine tested had given trace to 2 plus tests for reducing substance. It had therefore been felt that he exhibited low-threshold glycosuria (renal diabetes). He weighed 220 pounds at that time.

On admission to this unit his weight was 204 pounds, his height, 70 inches. The admission urine sample exhibited 2 plus copper reduction.

On the regular hospital regimen his blood glucose was 108 mg. per 100 c.c. two and one-half hours after the meal. One hundred gram oral glucose loading produced a 30 minute level of 107 and a two hour level of 115 mg. per 100 c.c. (Folin-Wu). Mild concomitant melituria was shown. A 24 hour sample showed a 1 plus Benedict's reaction, fermentation by yeast, and a positive resorcinol-HCl (Seliwanoff) * response for fructose. Eleven grams were present in 2,300 c.c. Polarimetric study of the urine showed levorotation. Routine multiple daily ward samples clinitested from trace to 3 plus, with an occasional negative reaction in large specimens.

The levulose tolerance was then determined.† (Figure 1.) A 15% fructopyranose solution which was glucose-free was given orally in a dosage of 0.5 gm. per kilogram of body weight. Both patient and control were postabsorptive by 15 hours prior to test zero. However, true sampling from the patient for two hours yielded 0.4 gm. urinary levulose. Furthermore, the fasting blood levulose level was 40.8 mg. per 100 c.c., in comparison to several milligrams in the control fasting blood sample. The 30 minute and the one, two and three hour figures were: 96.3, 122.0, 81.4, and 48.2 mg. per 100 c.c. The corresponding control figures were 18.5, 52.0, 18.5 and 4.0 mg. per 100 c.c. Urinary levulose excretion totaled 6.1 gm. for the patient (13.1% of the test load). In the control 0.47 gm. was present in the urine collected during the same three hour period (1.4% of the ingested fructose load).

The routine laboratory tests were negative. These included the hemogram, sedimentation rate, serology, and urinalysis apart from the Benedict's reaction. Liver function was assessed. The 5 mg. Bromsulphalein test, cephalin flocculation, thymol turbidity and van den Bergh were normal. Gall-bladder dye concentration and response were likewise normal. Renal assessment included phenolsulfonphthalein output of 37% in 15 minutes, with a 70% total two hour excretion, concentration to 1.030 after 12 hours, and a blood urea nitrogen of 10.4 mg. per 100 ml.

The minor complaint of dizziness, which the patient believed to be associated with diabetes, disappeared during the period of study.

DISCUSSION

Fructosuria, a rare and harmless metabolic anomaly, was first described in Europe in the 1870's and in the United States just prior to World War I. Lasker ⁸ developed evidence for a mendelian recessive-type inheritance of a group labeled "essential fructosuria." These are monomeliturias in which the urinary loss of fructose seems to be completely dependent upon its intake. The output is afructosuric when fructose is not available. The usual dietary sources of fructose include fruits and their products, some vegetables, and sucrose, which upon hydrolysis yields glucose and fructose. Ingestion of fructose by subjects having essential fructosuria results in the excretion of from 10 to 15% of the amount taken.

*Equal quantities of urine and 25% HCl are brought to a boil. Several crystals of resorcinol are added, and the mixture is again boiled for 10 seconds only. Fructose is present if a heavy red precipitate, soluble in alcohol, results.

† This experiment was performed in the Institute of Legal Medicine of the University of Wurzburg, Germany, through the courtesy of Professor Heinrich Saar. Blood fructose was determined by Stoehr's 1 method. Fructose, in contrast to glucose, rapidly reduces the phosphomolybdic acid reagent of Folin. The resultant blue reduction product is reoxidized to a colorless endpoint by titration in cold with standardized potassium permanganate. A protein-free blood filtrate, prepared by Hagedorn and Jensen's procedure as modified by Steinitz and Riesen, supplies material for simultaneous glucose and fructose determinations. Glucose interferes to a negligible extent, as calculated in Stoehr's procedure. Blood glucose was determined by the Folin-Wu method.

This patient excreted fructose. Fermentation, polarimetric, resorcinol-HCl and blood tolerance studies solidify this impression, and while the total absence of glucosuria was never proved, five negative glucose tolerance studies rule out the presence of diabetes.

Most unusual in this instance, however, is the postabsorptive fructosemia and fructosuria. It was as if a perfectly functioning regulator had been set ahead, for the mechanism dispatched the exogenous fructose load within three hours in as competent a manner as did that of the control. In contradistinction to the pattern of essential fructosuria, however, an endogenous residual was preserved by a return to the elevated starting level. By the time this level was re-attained, only 13% of the fructose load had been lost into the urine, excluding fecal loss. It would appear, therefore, that major utilization of the administered fructose was accomplished. One channel is suggested by the rise in blood glucose, actually to a level short of tolerance. Miller et al. found that two of three normal subjects exhibited an elevation of blood glucose following (intravenous) fructose

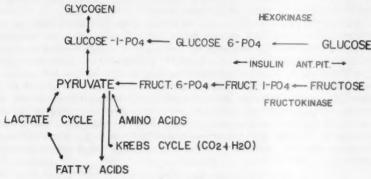


Fig. 2. Simplified scheme of Meyerhof-Embden theory.

administration. Such transformation occurs in the intestinal mucosa and in the liver.

Absorption of fructose as such from the gastrointestinal tract, as indicated by the ascendant portions of the tolerance curve, appears to have been prompt. Likewise does utilization of fructose (inferred from the rate of its disappearance) seem efficient above a certain blood level, but sluggish below this concentration.

The usual routes of utilization, beyond that into glucose, include an approach upon the pyruvate crossroads, as well as participation in liver and muscle glycogen formation.

Such an entry by fructose into the Meyerhof-Embden scheme may proceed through fructose-1-phosphate and fructose-6-phosphate.

To accomplish this transit, the evidence favors the existence of hexokinases separate from the glucokinases—in liver ⁵ as well as in muscle. ⁶ Cori et al. ⁵, ⁶ have termed these fructokinases. Speculation is tempting as to factors governing the activity of the fructokinases in this instance.

SUMMARY

An instance of fructosuria is presented. Spontaneous casual fructosuria occurred, in addition to an elevated fasting blood fructose level. The pattern of the fructose tolerance curve was apparently normal, although the initial and final levels were such as to exceed the "normal" renal threshold for fructose. The family history had suggested the presence of diabetes mellitus.

Whenever melituria presents itself in the presence of repeatedly normal glucose tolerance tests, fructosuria is a likely possibility. Fermentation, resorcinol-HCl, polarimetric and levulose tolerance studies are indicated. Such studies are not feasible on a mass scale, but for the individual exhibiting the above combination of findings, complete elucidation of the melituria is vitally important.

SUMMARIO IN INTERLINGUA

Un soldato de 20 annos de etate exhibiva spontanee melituria in despecto de al minus sex normal responsas de toleration de glucosa. Fermentation, tests a resorcinol e acido hydrochloric, e studios polarimetric identificava le substantia de reduction como fructosa (levulosa). In contrasto con le si-appellate fructosuria essential, iste fructosuria non dependeva del ingestion de fructosa o de substantias que cognoscitemente produce fructosa. Un controlate test del toleration oral de fructosa monstrava que le nivello sanguinee in stato jejun esseva 40 mg per 100 ml, in contrasto con 2 mg per 100 ml in le controlo. Le valor maximal de 122 mg per 100 ml esseva attingite post un hora, quando le controlo monstrava 52 mg per 100 ml. Al fin de tres horas, le nivello del patiente habeva descendite a 48 mg per 100 ml, durante que le nivello de controlo habeva retornate al norma. Simultaneemente le patiente monstrava un augmento de glucosa sanguinee. Nulle tal observation esseva facite in le controlo. Le studio pare indicar que le patiente ha un inefficace mechanismo de utilisation de fructosa e que iste mechanismo functiona solmente quando le nivello sanguinee de fructosa es alte.

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INTESTINAL POLYPOSIS AND ORAL PIGMENTATION: CASE REPORT*

By Roland W. Richterich-van Baerle, M.D., Boston, Massachusetts, W. W. Byrnes, M.D., Springfield, Massachusetts, Marshall G. Morris, M.D., and Saul Scheff, M.D., Boston, Massachusetts

"A very remarkable case of familial polyposis of the mucous membranes, of the intestinal tract, and the nasopharynx accompanied by peculiar pigmentation of the skin, and the mucous membranes" is the title of an article by Peutz.¹ The author described several members of a family with some or all of the manifestations of this unique syndrome. He felt that he was dealing with a new clinical entity of hereditary origin, and was able to demonstrate this syndrome in seven members of three generations of the same family, and to collect evidence that several others were probably afflicted.

Only five more cases $^{2, 3, 4}$ were reported between 1921 and 1949, when Jegher's and his associates 5 summarized all of the previous observations and added 10 more cases of their own. Since their exhaustive and scholarly review has focused the attention of more physicians on this syndrome not less than 25 well documented cases have been reported between 1949 and 1955 (table 1).

The publication of another case seems justifiable to us for two reasons. Patients afflicted with this entity are prone to develop serious complications (bleeding, intussusception and malignant degeneration), and most of them are hospitalized as emergencies. Awareness of this symptom complex will enable the physician to make a diagnosis on purely clinical grounds, and will help considerably to determine the extent of surgical intervention. Furthermore, it is of importance to record these strange and unexplainable associations of symptoms, since they represent rare "experiments of nature" which may, in a few years, help to elucidate some mechanisms of gene influence on the development of the various organs. This interest is enhanced by the fact that the intestinal polyps in this syndrome must be considered as premalignant lesions.

CASE REPORT

A 13 year old Negro schoolgirl was admitted to the Massachusetts Memorial Hospitals for the first time in August, 1955. She had been referred from the Out-Patient Department because of severe anemia and rectal bleeding.

Family History: There was no family history suggestive of any intestinal diseases. The mother and one male sibling, age 11, were examined clinically and by double contrast studies, with completely negative results. The parents of the patient were divorced, and no information on the father and his family could be obtained. Because of the early death of the mother's parents no information on her side was obtained either.

Personal History: For the last few years the patient had felt more tired than

^{*} Received for publication July 20, 1955.

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TABLE 1
Proved Cases of Intestinal Polyposis with Oral Pigmentation

Family History		200 0 11 100 0	27	570%
Malig- nancies		8	7	150%
Verified by	Endos- copy	2 1 2	10	
	Opera- tion	80000000000000000000000000000000000000	37	
	Colon Autopsy Opera-	2 %	S	
Polyps	Colon	-0	18	38%
	Small	222 23	45	%96
	Gastric	w === = = = .	6	190%
tation	Oral	P -0	39	830%
Pigmentation	Lips	raa-0	45	%96
×	Female	2	22	47%
Sex	Male	w w ~ ~ ~ ~	25	53%
No. of Cases		201011111111111111111111111111111111111	47	
Author		Peutz¹ Van Dijk and Oudenda¹² Foster³ Jeghers et al.⁵ Jeghers et al.⁵ Perry and Zuska³ Bradford³ Roux³ Roux³ Wolff³ Basu¹¹ Wolff³ Schaffer and Sachs¹¹ Schaffer and Feuchtwanger³? Young⁴ Kitchin³³ Rankin and Laird³³ Rankin and Laird³³ Froxell³ Rankin and Laird³³ Froxell³ Rankin and Laird³³ Reankin and Laird³³ Reankin and Laird³³ Reankin and Laird³³ Bertx and Bethell³¹ Rool and Guice³³ Richterich et al.³³	Total	Percentage
Case No.		11-7 18-9 18-9 13-22 13-22 25 25 25 26 27 28 30 31 33 33 33 34 34 40-42 44 45-46		

usual and had often had to stop playing. During the last year her weight had been constant at 74 pounds in spite of an adequate dietary intake. She was smaller than most of her classmates, measuring four feet nine inches.

Past History: The patient had had uncomplicated measles, mumps, chickenpox

and German measles, but no operations or previous hospitalizations.

Systemic Review: She complained of dyspnea on exertion, and progressive fatigue for the last few years, and had had enuresis all her life. She had not yet had her menarche.

Present Illness: During the two to three years prior to admission she had had frequent sharp midepigastric pain which did not radiate. The pain usually came on in the afternoon and persisted until she went to sleep. There was no relation to



Fig. 1. The duodenal polyp is seen in good relief.

food intake. During these painful episodes she felt nauseated, and vomited occasionally. These episodes occurred about once or twice a week. Two months prior to admission she had been seen at the Out-Patient Department, where a hypochromic anemia (hemoglobin, 9 mg.%) was found. She was treated with iron. One week prior to admission she was again seen at the Out-Patient Department, and examination showed that one out of five stool samples was 2 plus guaiac positive. She stated that one week prior to admission she had had a black formed stool. She also mentioned frequent spontaneous nosebleeds.

Physical Examination: Pulse, 72; blood pressure, 110/64 mm. of Hg; temperature, 99° F.; respiration, 18; weight, 74 pounds; height, four feet nine inches. She was a not obviously retarded but rather small, frail, undernourished Negro. Her skin was very darkly pigmented. The irises of her eyes were dark brown. Fundus was normal. Nose: the locus Hesselbachi was enlarged and reached almost to the floor of the nasal canal. There were numerous telangiectases in this area. Oral: slightly enlarged tonsils. Good teeth. On the hard and soft palates were numerous (approximately 50) dark brown pigment spots measuring about 1 mm. in diameter. There was no pigmentation of the lips, buccal mucosa or gums. Liver and spleen were not palpable. There was no pain or tenderness. Extremities: there was slight clubbing of the fingers and toes.



Fig. 2. The proximal ascending colon and ileocecal area is largely occupied by a rounded grouping of the broad-based lesions in the area.

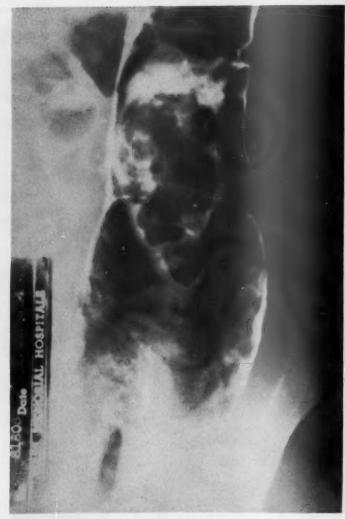


Fig. 3. A cluster of polyps in the mid-descending colon.

Laboratory:

- a. Chemical findings: Blood urea nitrogen, 8 mg.%; fasting blood sugar, 68 mg.%; total bilirubin, 0.3 mg.%; total protein, 6.1 gm.% (albumin, 3.0 gm.%; globulin, 3.1 gm.%).
 - b. Stools: Four out of eight tested stools were heavily guaiac positive.
 - c. Urine: Negative.
 - d. Hematology: Hemoglobin, 11 gm.%; hematocrit, 34.4%; red blood cells, 4.25

millions; mean corpuscular volume, 81 c μ ; mean corpuscular hemoglobin concentration, 32%; mean corpuscular hemoglobin, 25.9 $\gamma\gamma$; erythrocyte sedimentation rate (Wintrobe) corrected, 6 mm.; reticulocytes, 9.6%. Sickle cell test, negative. White blood cells, 6800/mm³; 64% polys; 2% band forms; 4% eosinophils; 36% lymphocytes; 6% monocytes. Platelets, 293,250. Clot retraction, 57.2%; serum expressed, 89.5%; prothrombin time, 13.5" (100% normal activity).

e. Electrocardiogram: Within normal limits.

f. X-rays:



Fig. 4. The cluster shown in figure 3 is seen in profile, with a single polyp just below and another just above at the splenic flexure.



Fig. 5. A large cluster and two smaller polyps in the over-distended sigmoid. A grouping of larger polyps is seen, with their free ends overlapping at the hepatic flexure.

Upper gastrointestinal tract: Esophagus within normal limits. Gastric mucosa prominent and tortuous. Pylorus intact. There was a large, pea-sized filling defect in the mid portion of the duodenal cap (figure 1). Study at frequent intervals failed to reveal any alteration in the function of mucosal pattern of the remainder of the small bowel. At three hours barium reached the transverse colon, and several radio-lucent areas were seen in the cecum.

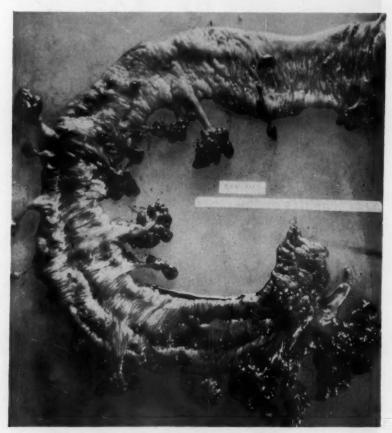


Fig. 6. The resected colon, revealing numerous polyps over its mucosal surface.

Barium enema: There were rounded filling defects in the descending and transverse colon, and a large, more irregular defect in the cecum (figure 2). Air contrast study revealed multiple polyps of the sigmoid (figure 5), colon and cecum. There was an intraluminal defect in the mid-descending colon (figures 3 and 4), representing either a large cluster of polyps or a huge single one. The entire x-ray examination was repeated, with duplication of these findings.

Chest: Negative.

Lumbodorsal spine: Spina bifida occulta at L.5.

Hands: The hands correspond to those of a female 13 years and three months old (Todd standard No. 29).

Hospital Course: The patient remained on the medical service for two weeks while the indicated studies were completed, and was treated with a bland diet and ferrous sulfate. She ate well and had no complaints.

Following her transfer to the surgical service proctoscopy was done (7"), and three large polyps arising from the posterior, anterior and right lateral wall of the rectum were removed and fulgurated. One small polyp was cauterized at 5", and five small sessile polyps were fulgurated at 4". Twelve days after transfer a laparotomy was performed and a polyp was removed from the first portion of the duodenum. The cecum and the ascending, transverse and descending colon were resected, and an end-to-end anastomosis between the ileum and the sigmoid was performed. The postoperative course was completely uneventful, and the patient was discharged 17 days following the operation.

Pathology Reports:

Rectal Polyps: Cauliflower-like tissue. Histologic examination: mucosal polyp with acute and chronic infection.

Duodenal Polyp: A 9 mm. piece of tissue of mulberry-like appearance. Histologic examination: polyp with patchy superficial acute and chronic inflammation of the duodenum.

Ileo-sigmoid (figure 6): 80 cm. of large bowel. Twenty-nine red-purple separate polyps, mostly on 2.5 cm. stalks were noted, many sharing a common stalk. The ileum was free of polyps. On the ileocecal valve a flat polyp was noted, more within the cecum than the ileum. Many of these polyps had a cluster-like appearance. The average measured 2 cm. by 1 cm. and had the character of a grape cluster. At least six of the polyps were on bifid stalks. Histology: multiple adenomatous polyps with patchy superficial acute and chronic inflammation of colon and duodenum. No evidence of malignancy.

DISCUSSION

It is not our intent to discuss the various features of this syndrome, since this has been done in an extensive and masterful way by Peutz ¹ and by Jeghers et al.⁵ Nevertheless, all cases reported have been summarized in a table (table 1) and, as can be seen, a total of 47 proved cases was found. Only those cases were included which had typical pigmentation and, in addition, intestinal polyps verified by autopsy, operation or biopsy. If all of the cases had been included which showed the pigmentation and indirect evidence of polyposis, e.g., family history, intussusception, bleeding, etc., the number of cases could have been doubled.

Most of the cases were discovered at operation for an abdominal emergency, especially intussusception. This complication is so common that several patients were operated upon two or three times before radical surgery was finally done. Another initial manifestation which might lead to the diagnosis is rectal bleeding. This was the reason for investigation in our case. The third and apparently the most important complication in adults is malignant degeneration of the polyps, which has been observed in about 15% of the cases reported.

The typical pigmentation consists of small, flat melanin spots, similar to freckles but without the same distribution. They appear on the lips, especially the lower one, on the skin of the nose, periorally, on the fingers and the toes. They are also observed on the buccal mucosa, the palate, the tongue, the gums, and occasionally the genital and rectal mucosa. The facial type of pigmentation has been observed in several families, and has been studied by Touraine and

Couder.⁴ Unfortunately, in most cases the intestinal tract was not investigated, so that we do not know if this pigmentation can exist alone as a hereditary entity. Jeghers,⁵ in his vast experience, has seen only one case of the typical pigmentation without associated intestinal polyposis.

The polyps are typically found in the small bowel but are also encountered in the stomach, the colon and, in rare instances, in the nasopharynx and the bladder. The only cases reported so far which did not have polyps in the small bowel were those by Touraine and Couder 4 and Troxell.⁶ Usually polyps can be found in several segments of the intestinal tract (table 1).

The hereditary aspects of the "disease" have been reviewed by Jeghers ⁵ who, after studying the several family trees available in the literature, came to the conclusion that the syndrome must be transmitted as a dominant gene of low penetrance. At least 27 of the 47 proved cases gave a history of suggestive symptoms in other members of the family. In most cases without a definite family history it was not possible to exclude the syndrome in blood relatives because of inadequate information. Therefore, it cannot be concluded that there are spontaneous cases. The peculiar association of pigmentation of certain parts of the skin, and premalignant polyposis of the gastrointestinal tract, can be explained only on the assumption of a pleiotropic gene.

The treatment of these patients depends entirely on the extent of adenomatous involvement of the intestine. If only single polyps are present, e.g., in the stomach, those should be removed. If the large intestine is affected, a resection of the afflicted segment is indicated.²⁵

SUMMARY

A case of intestinal polyposis and oral pigmentation in a 13 year old Negro girl is presented. The literature on the 47 reported proved cases of this syndrome is reviewed.

SUMMARIO IN INTERLINGUA

Es presentate un caso de polyposis intestinal con pigmentation del mucosa palatal in un 13-enne negra. Le patiente esseva hospitalisate a causa de sanguination in le intestino inferior e sever anemia hypochromic. Le roentgeno-examine del vias gastro-intestinal revelava polyposis del integre colon e del recto e le presentia de un polypo in le duodeno. Le historia familial del patiente esseva negative. Le mesmo vale pro studios roentgenologic del matre e del fratre del puera. Al operation, extense polyposis del colon e recto e un isolate polypo in le duodeno esseva trovate. Le polypos rectal e duodenal esseva fulgurate e le colon esseva resecate.

Le syndrome de polyposis intestinal e pigmentation oral ha recipite considerabile grados de attention in recente annos. Su diagnose ha devenite progressivemente plus frequente. Quaranta-quatro casos trovate in le litteratura es revidite, e le plus prominente characteristicas es summarisate in un tabula. Es includite in iste revista solmente casos establite per biopsia, operation, o necropsia. Le aspectos diagnostic e prognostic de iste entitate pathologic es discutite.

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INFECTIOUS MONONUCLEOSIS WITH JAUNDICE AND ABDOMINAL PAIN AS PRESENTING COMPLAINTS: REPORT OF CASE*

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An unusual case of infectious mononucleosis, in which jaundice and abdominal pain were the presenting complaints, was encountered at the Mayo Clinic. The purpose of this paper is to present and discuss this particular case.

CASE REPORT

A 46 year old white housewife was admitted to the Mayo Clinic on January 9, 1955, with a chief complaint of "pain in the abdomen" of seven days' duration. About two weeks prior to her admission the patient had been confined to bed for four days with a "flulike" syndrome of muscular aches and general malaise. She had returned to her normal activity until a week prior to admission, when she suddenly became nauseated and vomited while preparing food. The next day she vomited three times and noted a dull pain in the region of the umbilicus. Anorexia, occasional emesis, intermittent fever and abdominal pain continued until her admission to the clinic. The umbilical pain at times extended through into the left posterior lumbar region and occasionally into the left upper quadrant of the abdomen. She obtained some degree of relief by bending forward in a sitting position. Before coming to the clinic she had received penicillin and one of the sulfonamide drugs but had not shown improvement. She described her urine as being "a little darker" than usual, and her stools were light in color for three days preceding admission; her husband thought her skin might have been "a little yellowish." They were not aware of any illnesses characterized by jaundice in their neighborhood.

The patient had made several visits to the clinic, one of which was made in 1934; at that time she complained of "a lump in the neck." Examination had revealed only pharyngeal lymphoid hyperplasia and a few slightly enlarged cervical lymph nodes. In 1939 she had complained of pains in the left lower quadrant of her abdomen for which organic basis was not found. In 1941 she had complained of epigastric distress "similar to the present pain although not as severe." At that time roent-genograms of the gall-bladder and stomach did not show evidence of any abnormality. In 1950 she was again examined because of vague dyspepsia. Results of that examination were also within normal limits.

Physical examination on January 9, 1955, revealed a well developed woman who appeared acutely ill and slightly icteric. The blood pressure was 120 mm. of mercury systolic and 90 mm. diastolic; the pulse rate was 108 beats a minute and the oral temperature was 101.6° F. The patient's skin felt hot and dry. There was no significant lymphadenopathy. On examination the abdomen was found to be soft and without tenderness; no organs or masses were palpable. The impression formed by the examining physician was that the patient had atypical hepatitis, cholecystitis or pancreatitis.

* Received for publication June 25, 1955.

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Results of initial laboratory studies were as follows: 14.2 gm. of hemoglobin per 100 c.c. of blood; 4,230,000 erythrocytes and 6,500 leukocytes per cubic millimeter of blood, and a differential count of leukocytes showing 49.5% lymphocytes, 24.5% monocytes, 24% neutrophils, 1.5% eosinophils and 0.5% progranulocytes. Other studies on the blood revealed values as follows: 3.04 mg. of direct reacting bilirubin and 0.26 mg. of indirect reacting bilirubin per 100 c.c. of serum, 50.4 King-Armstrong units of alkaline phosphatase per 100 c.c. of serum, and a sedimentation rate of 39 mm. in the first hour (Westergren method). Serum lipase and amylase determinations gave results within normal limits. The result of the cephalin-cholesterol flocculation test was 4 plus, and a thymol turbidity test was graded 7.5 units. The prothrombin time (Quick) was 21 seconds. The results of urinalyses were within normal limits except for a positive reaction for bile. Roentgenograms of the thorax and abdomen did not show evidence of any abnormality. A heterophil antibody titer was 1:448 before absorption (guinea pig-kidney antigen) and 1:112 after absorption. A peripheral blood smear showed Downey cells characteristic of infectious mononucleosis. Peptidase measured 70 m_µ per milliliter of serum per hour (normal, 1 to 1.8), and the aldolase measured 0.95 mu per milliliter of serum per hour (normal, 0.47), which suggested the presence of severe damage to the parenchyma of the liver not due to extrahepatic obstruction.1 The Kline test gave negative results.

During the first week of hospitalization the patient had headaches, fever to 102° F., abdominal pain, anorexia, vomiting and mental depression, with mild confusion noted at night on two occasions. There were no abnormal findings on examination of the central nervous system. A few slightly enlarged posterior cervical lymph nodes were first noted on January 14. At times the patient required small amounts of Demerol for relief from umbilical pain and pain in the left upper quadrant. Rest in bed was strictly enforced and she was served a high protein diet, for which she initially demonstrated little appetite. Daily intravenous infusions of 2,000 c.c. of 5% glucose in distilled water were administered, along with vitamins B₁₂ and K, and a preparation of multivitamins by mouth. The vitamin B₁₂ was administered in doses of 30 µg daily and was given in an attempt to combat the patient's anorexia.2 A mild hemolytic phenomenon was suspected on January 19 because of a rise in indirect reacting bilirubin from 0.26 to 1.13 mg. per 100 c.c. of serum, associated with deepening jaundice, which occurred coincidentally with a fall in hemoglobin from 14.5 to 11 gm. The reticulocytes at this time were 2.6% and later rose to 4.8%. A smear of peripheral blood made on January 20 showed, in addition to Downey cells, polychromasia and occasional basophilic stippling. The antiglobulin (Coombs) test was negative. On January 21 acute follicular membranous tonsillitis and pharyngitis were evident. A few axillary nodes were now palpable. On January 22, after the patient had complained of severe pain in the left upper quadrant extending into the interscapular area, the spleen became palpable for the first time. It felt quite soft and tender. The liver was palpable four days later. The patient improved rather rapidly after the onset of pharyngitis. She became afebrile after the first week in the hospital. She was discharged February 4, 1955, 27 days after her admission, to convalesce at home. At that time she was free of pain and jaundice, and the value for serum bilirubin had returned to normal. A Bromsulphalein liver-function test done shortly before her dismissal did not show retention of dye at the end of one hour. The value for alkaline phosphatase, which had reached a maximum of 91.2 King-Armstrong units on January 17, had also returned to normal, and the heterophil antibody titer, which had reached a maximum of 1:4,096 before absorption and 1:448 after absorption on January 13, had dropped to 1:2,048 before absorption and 1:112 after absorption.

At the time of reexamination on February 25 the patient felt well except for some aching in the legs. The liver and spleen were not palpable. Laboratory data

included determinations of direct and indirect reacting serum bilirubin, which were negative, and 0.74 mg. per 100 c.c. of serum, respectively. The value for alkaline phosphatase was 12.6 King-Armstrong units per 100 c.c. of serum; the cephalin-cholesterol and thymol turbidity tests were read as 3 plus and 6 units, respectively, and nothing abnormal was noted on the cholecystogram.

On April 27 the patient felt entirely well. Results of physical examination were within normal limits. Laboratory data included determinations of direct and indirect reacting serum bilirubin, which were negative, and 0.52 mg, per 100 c.c. of serum, respectively. Results of the cephalin-cholesterol and thymol turbidity tests were read as negative and 2 units, respectively. Bromsulphalein was not retained in the serum at the end of one hour.

COMMENT

Initially, this patient presented a considerable problem in differential diagnosis. The onset of her illness, with anorexia, vomiting, and flulike complaints, suggested infectious hepatitis. The severity of the abdominal pain, however, was not in keeping with this diagnosis and suggested the possibility of disease of the biliary tract or even pancreatitis. Studies of liver function did not clarify the situation, since the positive results of tests for cephalin-cholesterol flocculation and thymol turbidity were indicative of hepatocellular disease, while the markedly elevated alkaline phosphatase suggested obstruction of the biliary tract. The latter finding, plus the presence of severe abdominal pain, even led us to consider the possibility of obtaining consultation from a surgeon. It was only by determination of the heterophil antibody titer that the true nature of the patient's illness became apparent.

Gloyne ³ has reported a case somewhat similar to ours, studied by means of serial biopsies of the liver. The presence of jaundice and the similarity to infectious hepatitis have been noted in other cases ⁴⁻⁹ of infectious mononucleosis. Abdominal pain also has been noted by others, ^{6, 10-12} but the combination of jaundice and abdominal pain must be unusual in this disease. The relief of pain by leaning forward in a sitting position has been described by Perisho and Sargent. ¹² The cause of the abdominal pain in infectious mononucleosis is not definitely known. Pain in the right upper quadrant could be attributed to stretching of Glisson's capsule. Pain in the left upper quadrant, such as was experienced by our patient and also noted by Walker, ¹³ might be due to an enlarging spleen.

An unusual feature in our case was the degree of elevation of the serum alkaline phosphatase. In a review of the recent literature, no higher level for this substance was found recorded for patients with infectious mononucleosis. A value of 60 King-Armstrong units was recorded in a case in which the disease was fatal. Some degree of elevation of the serum alkaline phosphatase, however, occurs in a high percentage of cases of infectious mononucleosis, among both jaundiced and nonjaundiced patients. Jordan and Albright found elevated levels in 38% of 20 patients who were tested, and they reviewed other studies in which elevations occurred among 43 to 88% of the patients who were tested. Gall determined the values for serum alkaline phosphatase for 34 patients who had infectious mononucleosis, one of whom was jaundiced. He found hyperphosphatasemia in 29 patients but could not find a satisfactory explanation for it. Concentrations of serum alkaline phosphatase in excess of 30

King-Armstrong units, or of 10 Bodansky units, are commonly associated with obstruction of the biliary tract. The case reported herein is a testament to the error of relying too strongly on this observation, but the error has been even more emphatically exposed by Gall's ¹⁶ series in which six patients demonstrated levels in excess of 30 King-Armstrong units, and four patients had levels greater than 10 Bodansky units. In eight of 12 cases Peterson ¹⁷ found levels in excess of 10 Bodansky units.

It has been well demonstrated that the results of one or more than one of the tests for liver function may be abnormal in an extremely high percentage of both jaundiced and nonjaundiced patients having infectious mononucleosis.^{5, 7, 13, 13, 15-21} Jaundice occurs probably in about 5% of cases.⁷ A case of severe jaundice of 11 weeks' duration ²² and a case of cirrhosis developing subsequent to jaundice associated with infectious mononucleosis ²³ have been recorded. Acute hepatic failure with subsequent death has been noted.^{14, 24} In the vast majority of cases, however, although involvement of the liver in infectious mononucleosis produces abnormal pathologic findings and results for tests for liver function.

it does not result in permanent hepatic disability or dysfunction.

Hepatic involvement of infectious mononucleosis, as revealed by biopsies of the liver at various stages of the disease, 25, 26 and by studies at necropsy, 27-31 apparently is similar to that of infectious hepatitis. Wadsworth and Keil 25 indicated that the histologic changes in the liver in infectious mononucleosis are indistinguishable from those of infectious hepatitis. Other investigators,26 however, found scattered focal infiltrations which they considered to be helpful in differentiating atypical cases of infectious mononucleosis from infectious hepatitis. Proliferative changes in the epithelium of the bile duct also have been found in cases of infectious mononucleosis. Custer and Smith 27 described "minor bile duct proliferation in addition to periportal lymphocytic infiltration." Gloyne 3 obtained a specimen of liver for biopsy, at the height of the rise in alkaline phosphatase (29 Bodansky units), which showed "large cells . . . packing a number of the sinusoids . . . (an) apparently atypical endothelial proliferation." Gloyne concluded that "the findings were principally those of diffuse hepatocellular damage plus obstruction in the biliary radicles." Kilham and Steigman 32 obtained a specimen of liver for biopsy from a deeply icteric patient (alkaline phosphatase, 26 Bodansky units), which showed "a welldeveloped histiocytic reaction with some early proliferation of bile ducts." Sharp 30 noted at necropsy that "the bile duct epithelium was swollen, sometimes obliterating the lumen." In 1946 Wechsler and associates 6 concluded that the jaundice of infectious mononucleosis was "due to a diffuse hepatitis which is accompanied by an obstruction of the bile capillaries."

It has been suggested that the proliferative changes in the intrahepatic bile ducts might explain the elevation of serum phosphatase. The fact that infectious hepatitis and infectious mononucleosis may be clinically indistinguishable has led Clough of to speculate on the possibility of similar etiology. However, Berk and co-workers of could not find a diagnostic level of absorbed heterophil antibodies in infectious hepatitis. Leibowitz of serologic absorption tests in the diagnosis of infectious mononucleosis. In 1954 Rubin of described a difference in the serum lipoprotein fractions in the two diseases as determined by

ultracentrifugation. Examinations of blood smears of patients with infectious hepatitis fail to reveal Downey cells characteristic of infectious mononucleosis.

Many authors ⁸⁶⁻⁴⁸ have reported hemolytic phenomena in cases of infectious mononucleosis. Some ^{88, 41} have reported positive results for antiglobulin tests; others ^{36, 43} have described increased fragility of erythrocytes. In our case hemolysis offered no serious problem. In other cases ^{89, 40, 48} it has been severe, and in one ⁸⁷ splenectomy was necessary. The basis for the hemolysis remains in doubt, but Wilson and associates ⁸⁷ and Hall and Archer ⁴² speculated on a possible effect of "hypersplenism." Hypersplenism is suggested by the occasional occurrence of thrombocytopenic purpura, ^{44, 45} pancytopenia, ⁴⁶ agranulocytosis ⁴⁷ and the frequent occurrence of splenomegaly (43%)¹¹ among patients having infectious mononucleosis. Rupture of the spleen, indeed, seems to be the most frequent cause of death in infectious mononucleosis.⁷

SUMMARY

A case of infectious mononucleosis, encountered at the Mayo Clinic, is presented. Jaundice and abdominal pain were the presenting symptoms at a time when pharyngitis and enlargement of lymph nodes had not yet appeared. This combination of symptoms, together with the finding of a markedly elevated value for serum alkaline phosphatase, suggested the diagnosis of disease of the extrahepatic biliary tract. On the other hand, the prodromal symptoms of the patient's illness and the positive results for cephalin-cholesterol flocculation and thymol turbidity tests suggested infectious hepatitis. It was only by the determination of the heterophil antibody titer that the true nature of the patient's illness became apparent. While involvement of the liver is common in infectious mononucleosis, the combination of jaundice and severe abdominal pain is an unusual occurrence.

SUMMARIO IN INTERLINGUA

Es presentate un caso inusual de mononucleosis infectiose, incontrate al Clinica Mayo. Jalnessa e sever dolores abdominal esseva le symptomas de presentation in un adulte patiente feminin a un tempore quando pharyngitis e allargamento del nodos lymphatic habeva non ancora apparite. Iste symptomas de presentation, insimul con le constatation de un marcate elevation del valor de phosphatase alcalin in le sero, suggereva le diagnose de morbo del extrahepatic vias biliari. Del altere latere, le symptomas prodromal e le resultatos positive del test de flocculation a cephalinacholesterol e del test de turbiditate a thymol suggereva le diagnose de hepatitis infectiose. Un exploration chirurgic esseva prendite in consideration, sed le ver natura del morbo del patiente deveniva apparente per le determination del titro de anticorpore heterophilic.

Le implication del hepate es un occurrentia commun in mononucleosis infectiose, ben que le combination de jalnessa con dolores abdominal es inusual. Le valores del phosphatase alcalin del sero es a vices elevate in casos de mononucleose infectiose. Le rationes pro iste elevate valores non es clar.

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EDITORIAL

THE Rh-Hr TYPES; A COMPLEX PROBLEM IN SEROLOGY, GENETICS, AND NOMENCLATURE

THE situation with which the student of blood grouping is confronted today is incomparably more complex than that which existed 25 years ago. Yet, even when only the four blood groups were known, the facts were not entirely clear, and a controversy raged among workers in the field regarding the mechanism of heredity and a suitable method of designating the blood groups.1 The genetic controversy was settled when Bernstein's theory of inheritance of the blood groups by multiple allelic genes was adopted as scientifically correct. Bernstein's theory has survived to the present time and is applied daily in medicolegal cases of disputed paternity.^{2,3} The nomenclature problem was less easily resolved, because of the attractive though deceptive simplicity of the numerals I, II, III, IV for designating the blood groups. The existence of two competing systems of numbering failed to disturb most workers in the field.4 It was only the exigencies of World War II which caused the Moss and Jansky numberings to be discarded, and led to the universal adoption of the International A-B-O Nomenclature.

One might imagine that the experience with the A-B-O groups would have helped forestall the present controversy regarding the Rh-Hr types. As already mentioned, however, the Rh-Hr problem is considerably more complex, and the issues are somewhat different so that the basic principles at stake have become obscured. The demonstration that the Rh-Hr tests could be used in cases of disputed paternity where they greatly increase the chances of excluding a falsely accused man brought the matter to a head.⁵ Judges, attorneys, and juries unfamiliar with blood group serology and genetics suddenly found themselves confronted with a mass of complex reports. Confusion was compounded by the conflicting terminologies which left both bar and bench bewildered. This situation prompted the Committee on Medicolegal Problems of the American Medical Association to prepare a report in which it was recommended that for medicolegal purposes the original Rh-Hr terminology be used exclusively.6 Since this position is not

¹ Wiener, A. S.: Blood groups and transfusion, 3rd ed., 439 pp., 1943, C. C Thomas, Springfield, Illinois.

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⁴Kennedy, J. A.: Blood group classifications used in hospitals in the United States and Canada, J. A. M. A. 90: 1323-1324, 1928; 92: 610-615, 1929.

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acceptable to many workers in the field, this recommendation has so far been published only as a tentative report. It is the purpose of this editorial to review the development of the knowledge of the Rh-Hr types, with special reference to the problem of nomenclature.

In his classic book on the specificity of serological reactions, Landsteiner 7 pointed out that antibodies are characterized not only by their specificity but also by their ability to cross-react. In fact, crossreactivity is just as characteristic a property of antibodies as specificity, and Landsteiner made use of both these properties in his pathfinding studies of the chemical basis of serological specificity. In describing the reactions of antibodies and antigens he applied the lock and key analogy used by Emil Fischer for enzyme specificity, and showed that antigens of simple chemical structure can combine with a multiplicity of antibodies. The characteristics of the surface of the antigen molecule which enable it to combine with its antibodies have been given the name of serological "factors" of the antigen. Since, in general, each antigen has multiple corresponding antibodies, so it is that each antigen has an equal number of hypothetical factors. This concept is of basic importance for the understanding of the serology of the Rh-Hr blood types, and for that matter also the A-B-O blood groups and the M-N types.9

It is interesting that the first and still most important Rh factor, now designated as Rho, was discovered by a method that makes use of the cross-reactivity of antibodies. Landsteiner and Wiener 10 injected the blood of rhesus monkeys into rabbits and guinea pigs and produced antisera which clumped human blood cells containing the factor now known as Rho, but did not clump blood cells lacking this factor. This is mainly of historical interest because more satisfactory anti-Rh sera are readily obtained from Rh-negative human donors who have been deliberately sensitized or who have become sensitized by blood transfusion or pregnancy. A seeming paradox is the fact that the human anti-Rho sera, despite high titer and potency, fail to react with rhesus monkey blood cells. The nonreciprocal nature of the reactions of antirhesus serum and human anti-Rho serum was not entirely unexpected, since it would be hardly likely for the antigens in rhesus monkey red blood cells and human red blood cells to be identical. On the other hand, such non-reciprocal reactions are unintelligible if one postulates a simple one-to-one correspondence between antigen and antibody.

Study of human anti-Rh sera showed that while most of them gave parallel reactions, there were occasional discrepancies, indicating that there was more than one kind of Rh factor. The first of these dis-

⁷ Landsteiner, K.: The specificity of serologic reactions, Rev. ed., 310 pp., 1945, Harvard Press, Cambridge, Mass.

Press, Cambridge, Mass.

⁸ Wiener, A. S.: An Rh-Hr syllabus, 82 pp., 1954, Grune & Stratton, New York.

⁹ Wiener, A. S., and Wexler, I. B.: The mosaic structure of red blood cell agglutinogens, Bact. Rev. 16: 69-87, 1952.

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covered 11 is now known as rh'. (The small r is used to indicate the lower antigenic potency of this factor than Rho, so that it is much less often involved in clinical problems.) A second related Rh factor 12 is designated as rh". At almost the same time Levine et al. 13,14 described a human antiserum which gave reactions in part reciprocal to those of the Rh antisera, for which he therefore suggested the designation anti-Hr. It is now known that there are a number of such anti-Hr sera and since the Hr factor originally found has been shown to be reciprocally related to the factor rh' it is now known as hr'. Mourant 15 described for the first time anti-hr", but to date there is no convincing evidence for the existence of anti-Hro. At present, many more Rh-Hr factors are known to exist, but the three Rh factors and the two Hr factors mentioned above have been studied most intensively.

That the various Rh-Hr factors are related to one another was evident from their association in studies on the distribution of the Rh-Hr factors in the population. Further light was thrown on the subject by genetic studies. 16,17 In families where one parent is Rh negative and the other has the two factors Rho and rh' it was observed that either all of the children had both factors or half of the children had both factors and the other half had neither. With this may be contrasted the situation in the A-B-O groups where in the mating AB × O half the children are group A and half group B. Thus, in families where one parent has the two properties A and B these properties will always separate so that each child inherits either A or B but not both from this parent. On the other hand, when a parent has the two factors Rho and rh', these factors generally stay together so that each child inherits either both factors or neither. Thus, while A and B are properties of separate agglutinogens, **Rh**_o and **rh**' may be properties of one and the same agglutinogen. This agglutinogen which has the two factors Rho and rh' has been designated agglutinogen Rh_1 , and the corresponding gene R^1 . Thus, the families could be of two kinds, namely $R^1R^1 \times rr$, in which all the children would be type Rh₁, or $R^{1}r \times rr$, where half the children would be type Rh₁ and half would be Rh negative. Subsequently, it was found that agglutinogens exist which have factor Rho alone and factor rh' alone so that occasional type Rh₁ individuals may be of genotype $R^{\circ}r'$. In rare matings with this type, namely $R^{o}r' \times rr$, half the children will have

¹¹ Wiener, A. S.: Hemolytic reactions following transfusion of blood of the homologous group. II. Further observations on the role of Rh particularly in cases without demonstrable antibodies, Arch. Path. 32: 227-250, 1941.

¹² Wiener, A. S.: Distribution and heredity of variants of the Rh types, Science 93: 182-

¹⁸ Levine, P., Burnham, L., Katzin, E. M., and Vogel, P.: The role of isoimmunization in the pathogenesis of erythroblastosis fetalis, Am. J. Obst. and Gynec. 42: 925-944, 1941.

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factor Rho alone and half will have rh'. It is not difficult to incorporate into the scheme the subsequently discovered factor rh", and in 1943 Wiener 18 described the eight Rh types determined by the three factors Rho, rh' and rh" and their corresponding genotypes. To this scheme were later added the additional factors hr', hr', rhw, hr and others, which although they increase the complexity considerably contribute no new fundamental principles.

The observations in families and on the distribution in the general population led to the concept of inheritance of the Rh-Hr types by multiple allelic genes, and the most important genes identified to date are Ro, R1, R1w, R2, Rz, r, r', r'w, r'' and rv. All published studies corroborate this theory, 19,21 so that the Rh-Hr tests are routinely applied in clinical medicine for predicting the probable Rh-Hr type of the unborn baby in families with sensitized Rh-negative mothers, and in medico-

legal cases of disputed parentage.

Early in the studies,1 evidence had already been found to refute the concept of separate pairs of allelic genes for the factors Rho, rh', hr', rh" and hr". Still the facts presented have been interpreted in this manner. According to this second interpretation^{20,21} the antigenic factors rh' and hr', alternatively designated as C and c, respectively, are considered to be a pair of agglutinogens inherited by means of a corresponding pair of allelic genes C and c. Similarly factor Rho was designated as agglutinogen D, and factor rh" as agglutinogen E, and it was predicted that contrasting agglutinogens for these would be found, namely, d and e. The three pairs of allelic genes that controlled the inheritance of these three factor pairs were supposed to be linked in a single pair of chromosomes, so that in place of the multiple alleles of Wiener's hypothesis were substituted sets of closely linked genes of the Fisher-Race hypothesis: r = cde, r' = Cde, r'' = cdE, $r^{\nu} = \text{CdE}$, $R^{o} = \text{cDe}, R^{1} = \text{CDe}, R^{2} = \text{cDE}, \text{ and } R^{z} = \text{CDE}.$ The discovery by Mourant 16 of anti-hr" (anti-e) was hailed as confirmation of this concept, especially when shortly thereafter the discovery of anti-Hro was announced. Because of these reports and the attractive simplicity of the scheme, which implied a one-to-one correspondence between gene, agglutinogen and antibody, the concept had considerable appeal and gained immediate widespread adoption.

The apparent success of this simpler C-D-E concept was shortlived, however. While the existence of anti-hr" has been confirmed a number of times, the existence of anti-Hro has not, and the early reports appear

¹⁸ Wiener, A. S.: Genetic theory of the Rh blood types, Proc. Soc. Exper. Biol. and Med. 54: 316-319, 1943.

Wiener, A. S.: Rh-Hr blood types. Applications in clinical and legal medicine and anthropology, 763 pp., 1954, Grune & Stratton, New York.
 Fisher, R. A., cited by Race, R. R.: An "incomplete" antibody in human serum, Nature (London) 153: 771-772, 1943.

⁸¹ Race, R. R., and Sanger, R.: Blood groups in man, 2nd ed., 400 pp., 1954, Blackwell Scientific Publ., Oxford.

to have been in error. Moreover, intensive investigation of human antisera from patients who had hemolytic transfusion reactions or who had had erythroblastotic babies, disclosed the existence of antisera of different but related specificities, indicating a much greater complexity of the Rh-Hr system than could be accommodated to the C-D-E hypothesis. The simple scheme, Cc, Dd, Ee, made no allowance for such new factors as rhw, rhz, hr, hr, hr, or the so-called intermediate factors 22 of which the most important is $\Re h_0$. Certain exceptions to the postulated inheritance of Rh-Hr factors in triplets made it necessary to invoke the concept of chromosome deletions 23; yet individuals supposedly homozygous for deletions were perfectly normal while in animals deletions prove to be invariably lethal. When crossing over among C, D, and E could not be demonstrated, the concept of complete linkage was invoked, and sets of linked genes such as CDeF were treated as a unit like R1, so that the distinction from the multiple allele theory disappeared. In fact, the proponents of the linked gene theory have adopted so-called shorthand notations, which are merely an early form of the Rh-Hr symbols, thus bringing the entire matter back to multiple allelic genes in full circle.24

Despite these developments, the C-D-E-F notation has retained most of its popularity on the basis that it is simpler to teach than the Rh-Hr nomenclature. Admittedly, the facts that have been established concerning the Rh-Hr types are highly complex, but those who wish to work in the field must master them. Since the notations, whether Rh-Hr or C-D-E, merely translate these complex facts into symbols, the nomenclature should present no problem. For workers who understand the subject the choice of notation is made not on the basis of ease of teaching, but depends instead on which set of symbols more accurately mirrors the actual relationship existing among the Rh-Hr genes, blood factors, and agglutinogens.25

> A. S. WIENER I. B. WEXLER

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 Wiener, A. S. and Woyler, J. P. The interpretation of bland general contents.

¹⁶ Wiener, A. S., and Wexler, I. B.: The interpretation of blood group reactions, with special reference to the serology and genetics of the Rh-Hr types, Novant Anni delle Leggi Mendeliane, edited by L. Gedda, pp. 147–162, 1956, Istituto Gregorio Mendel, Rome.

REVIEWS

Human Physiology. By F. R. WINTON, M.D., D.Sc., and L. E. BAYLISS, Ph.D. 4th Ed. 616 pages; 16 × 24.5 cm. Little, Brown and Co., Boston. 1955. Price, \$8.00.

This basic text in physiology, which first appeared in 1930, is now available in its fourth edition, an impressive demonstration of its durability in the academic community. The format has been little changed through the years and a substantial portion of the original illustrations are still in use, although many new and appropriate ones have been added. These are all carefully and skillfully executed. The text has been fully revised and brought up to date and each section written by an authority in the field. Careful editing has preserved a uniformity in style, which is simple and easy reading, one of the book's most appealing recommendations. There are relatively few tables and charts and when they do appear they are clearly drawn

and easy to grasp.

The revision is up to the minute and includes adequate discussions of the recent advances. Inclusion of material on aldosterone and nor-adrenaline attests to this fact, as well as a comprehensive discussion of the modern ideas on the control of breathing, humoral control of urine formation, hypothalamic influences on hormone secretion, cortical localizations and many others. All in all the neophyte in physiology could hardly do better and the book is highly recommended to those who want a comprehensive, accurate summary of current physiological thinking. Probably it will be of greater value to the medical student who is in the process of acquiring his physiological background than to the established clinician who wants to brush up on the fundamentals. As is the case with most British texts, there is little discussion of clinical matters except when they illuminate the basic physiology. If any criticism is in order, it is perhaps that an undue emphasis has been placed on the nervous system, which seems to be somewhat out of balance with the rest of the book. An excellent bibliography of monograph and review articles, listed by subjects, adds greatly to the value of the book.

DIETRICH C. SMITH

Diagnosis of Congenital Heart Disease: A Clinical and Technical Study by the Cardiologic Team of the Pediatric Clinic, Karolinska Sjukhuset, Stockholm. By Sven R. Kjellberg, Edgar Mannheimer, Ulf Rudhe and Bengt Jonsson. 649 pages; 18.5 × 26.5 cm. Year Book Publishers, Inc., Chicago, Ill. 1955. Price, \$22.00.

The authors of this book comprise a team consisting of two cardiologists and two roentgenologists who evaluated 396 cases of congenital heart disease. This book is unusual for the clarity of the numerous photographs, particularly the angiocardiograms. There are 581 excellent figures and an extremely valuable bibliography of almost 400 references. In most instances the patients were evaluated by means of cardiac catheterization, angiocardiography, phonocardiography, electrocardiography and electrokymography. The literature has been reviewed for each entity discussed. Included in the text are chapters devoted to embryology, roentgenology, anatomy and physiology of the heart, a description of the various diagnostic technics and chapters devoted to specific congenital lesions.

The text fills what has hitherto been a gap in the literature on congenital heart disease. It is an extremely valuable correlative text that should be a reference volume to roentgenologist, cardiologist, and students.

L. S.

Atlas und Kurzgefasstes Lehrbuch der Phonokardiographie und verwandter Untersuchungsmethoden. By Priv.-Doz. Dr. Med. K. Holldack and Dr. med. D. Wolf. 171 pages; 20.5 × 28.5 cm. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, Ganzleinen DM 49.50.

The phonocardiographic demonstration of heart sounds and murmurs has proved itself a most valuable tool for the teaching, learning and understanding of cardiac auscultation. In an introductory chapter the basic principles for the graphic recording of auscultatory phenomena are very well defined. Especially well done is the section on filter and filter design with graphs demonstrating the system developed and applied by the authors. The work of the Swedish, British and German investigators was unquestionably facilitated by the availability of superb instruments with multichannel recording of up to eight channels simultaneously, with photographic or "direct" recording systems. The Swedish Elmquist and German Schwarzer machines have in addition well designed band filter systems. The quality of the reproduced graphs speaks adequately for the performance of the instruments.

The descriptive section of the book is most informative and clearly written and well supplied with illustrations which clearly demonstrate the point under discussion. Some of the observations on murmurs and sounds in mitral disease are most interesting and the discussion stimulating.

Print, paper, reproduction of diagrams and graphs are excellent. The text is clearly and concisely written. The book is recommended to any student of phonocardiography.

A. G.

Lehrbuch der Verdauungskrankheiten. 2nd, improved Ed. By Prof. Dr. Med. Norbert Henning, Direktor der Medizinischen Universitätsklinik in Erlangen; unter röntgenologischer Mitarbeit von Doz. Dr. Med. Walther Baumann, Krankenanstalten Bethel bei Bielefeld. 562 pages; 24.5 × 17.5 cm. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, Ganzleinen DM 77.— (approximately \$18.35).

For the preparation of this second edition of their textbook of gastroenterology the authors have obtained as collaborators Dr. Hans Kinzlmeier for the chapter on diseases of the stomach, Dr. Ludwig Demling for the chapter on diseases of the liver and the biliary pathways, and Dr. Klaus Heinkel for the chapter on diseases of the pancreas. The other main chapters deal with diseases of the oral cavity and the salivary glands, diseases of the esophagus, diseases of the intestine and diseases of the peritoneum. Of the 335 illustrations, 35 are in color. Compared with the first edition of 1949 (which had 799 pages), the text has been shortened in many instances while the scope of the book has been broadened. For many methodical details or discussion of surgical aspects the reader is now referred to the first edition.

The book represents a well integrated cooperative enterprise of the Medical Clinic of Erlangen University. The roentgenograms are of special interest because of the many fine relief pictures of gastric and intestinal mucosa which were obtained by Dr. Baumann's technic of using only small amounts of barium sulfate suspension

initially. All roentgenographic reproductions and endoscopic photograms are supplied with a separate and concise explanatory text which is a welcome help to the reader.

Dr. Henning who wrote his first textbook on gastroscopy in 1935 (Lehrbuch der Gastroskopie, Johann Ambrosius Barth, Leipzig), stresses the use of various endoscopic procedures, in the development of which he has been quite active over a period of more than 20 years. Twelve illustrations deal with the esophagoscope, dilators of the cardia, various gastroscopes, the laparoscope, the rectosigmoidoscope and the proctoscope. Many optical and photographic improvements are mentioned. It is regrettable that not more of the endoscopic pictures are offered in color.

The entire text, which is dedicated to the late internist Professor Paul Morawitz of Leipzig, maintains the traditional German standards of earnest clinical research, teaching and therapeutic effort. Remarkable are the painstaking details on gastric and intestinal analysis, stool examinations, liver and pancreas function tests and dietary therapy. There is little physiologic chemistry in the book; the only structural formulae shown are those of bilirubin and cholesterol. Dr. Demling mentions the progress in the chemical identification of urinary and fecal metabolites of bilirubin which has brought on the current controversy in the physiological and clinical interpretation of the appearance and formation of stercobilin/stercobilinogen versus urobilin/urobilinogen. What was formerly determined as urobilinogen and urobilin in the normal urine by Ehrlich's and Schlesinger's reactions, is actually stercobilinogen and stercobilin. On the other hand, the normal production of urobilin bodies in the intestine is still probable and the enterohepatic circulation of urobilin has not been materially disproved.

As could be expected, the book lags behind in the knowledge of clinical tracer studies with radioactive isotopes. Only the indirect determination of gastric acidity with radioactive Ca⁴⁵ carbonate is mentioned. Furthermore one misses the great variety of therapeutic intravenous solutions which is available to the American physician.

The alphabetically arranged references to the literature, which have been listed separately on 22 pages, are precise and up to date in regard to the German and the international publications. But not every author or method mentioned in the text has been included.

Paper, printing and binding are of excellent quality. The book can be recommended for its clinical thoroughness and for its special combination of endoscopic and roentgenographic details.

ERNEST BRUCH, Ph.D., M.D.

Electrocardiography: Fundamentals and Clinical Application. 2nd Ed. By Louis Wolff, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital; Assistant Clinical Professor of Medicine, Harvard Medical School. 342 pages; 16.5 × 25.5 cm. W. B. Saunders Co., Philadelphia. 1956. Price, \$7.00.

This edition has added vectorial concepts of electrocardiography and a section on arrhythmias. The first portion is concerned with basic principles of electrocardiography and represents a most concise and lucid presentation of the fundamentals of electrophysiology. Vector principles are employed in the gradual development and clarification of electrical phenomena as regards the heart's anatomy and mechanism. Lead systems with uses, advantages, and interrelationships are clearly discussed with the use of vector concepts. Examples of variations of categorically abnormal tracings are used to demonstrate principles and elucidate the various changes which

may take place. Concepts which are frequently presented in a confusing manner are made clear. The clinical section includes basic standard, most often used criteria and might serve as a ready reference. Among the sections on abnormal electrocardiograms, the discussion of right ventricular hypertrophy is outstanding. The final section is devoted to cardiac mechanisms and alterations as produced by drugs. The less frequently encountered entities are also discussed. Numerous illustrations are included.

The vectorial approach is a welcome one to electrophysical aspects of electrocardiography and everyone should find it enlightening. It is highly recommended to the student of electrocardiography.

A. D. R.

The Behavior of Pulmonary Tuberculous Lesions: A Pathological Study. By E. M. Medlar, Chief Pathologist, Division of Tuberculosis, New York State Department of Health, Hermann M. Biggs Memorial Hospital, Ithaca, New York, etc. 244 pages; 26 × 17.5 cm. Monograph appeared as a supplement of the March, 1955, issue of the American Review of Tuberculosis, 1790 Broadway, New York. 1955. Price, \$2.50, cloth bound; \$1.50, paper-bound.

This monograph, representing the recapitulation of years of study in the field of pulmonary tuberculosis, deals with the pathologic manifestations of this disease process. A report of extensive research with laboratory animals is presented, in which the time sequence of tuberculous lesions is determined, and correlation with human disease is established. A summarization of findings from hundreds of human autopsies is submitted, showing reaction to the tubercle bacillus. Human pulmonary parenchymal and bronchial lesions are discussed, and the problem of bronchiectasis is evaluated. This work is copiously illustrated by 136 color photographs. These illustrations would be interpreted with great difficulty by a novice. The natural history of the tuberculosis lesion is well documented by the text. To those who have a basic knowledge of, and an interest in the morphologic progress of tuberculosis, this book is recommended as a useful reference.

C. F. C.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- Annual Epidemiological and Vital Statistics, 1953. Part I: Vital Statistics and Causes of Death. Part II: Cases of and Deaths from Notifiable Diseases. 571 pages; 28 × 21.5 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$10.00.
- Atlas of Exfoliative Cytology. Supplement I. By George N. Papanicolaou, M.D., Clinical Professor of Anatomy Emeritus, Cornell University Medical College. Pages not numbered consecutively; 28 × 20 cm. (loose-leaf). 1956. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, \$4.00.
- Clinical Urology (in two volumes). 3d Ed. By OSWALD SWINNEY LOWSLEY, A.B., M.D., F.A.C.S., F.I.C.S., Diplomate of American Board of Urology, etc.; and

- THOMAS JOSEPH KIRWIN, M.A., M.S., M.D., F.A.C.S., F.I.C.S., Diplomate of American Board of Urology, etc.; drawings by WILLIAM P. DIDUSCH. 999 pages (total, both volumes); 29 × 22.5 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, \$32.50.
- Cryptococcosis: Torulosis or European Blastomycosis. By M. L. LITTMAN, M.D., Ph.D., Department of Microbiology, The Mount Sinai Hospital, New York; and LORENZ E. ZIMMERMAN, M.D., Central Laboratory, Veterans Administration, Armed Forces Institute of Pathology, Washington, D. C. 205 pages; 26 × 18 cm. 1956. Grune & Stratton, Inc., New York. Price, \$8.50.
- Diagnosis and Treatment of Peripheral Vascular Disorders. By David I. Abramson, M.D., F.A.C.P., Professor and Head of the Department of Physical Medicine and Rehabilitation, and Professor of Medicine, University of Illinois, College of Medicine, etc. 537 pages; 26.5 × 17.5 cm. 1956. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, \$13.50.
- A Doctor's Marital Guide for Patients, Written for Those Married or About to Be Married. By Bernard R. Greenblat, B.S., M.D., Associate Attending, Obstetrics and Gynecology, Kings County Hospital, Brooklyn, N. Y., etc. 88 pages; 17,5 × 13.5 cm. (paper-bound). 1956. The Budlong Press, Chicago. Price, \$1.50.
- A Doctor's Marital Guide for Patients, Written for Those Married or About to Be Married: Catholic Edition. By Bernard R. Greenblatt, B.S., M.D., Associate Attending, Obstetrics and Gynecology, Kings County Hospital, Brooklyn, N. Y., etc. 88 pages; 17.5 × 13.5 cm. (paper-bound). 1956. The Budlong Press, Chicago. Price, \$1.50.
- The Drug Addict as a Patient. By Marie Nyswander, M.D., Senior Supervising Psychiatrist, Post Graduate Center for Psychotherapy, etc. 179 pages; 22.5 × 14.5 cm. 1956. Grune & Stratton, New York. Price, \$4.50.
- Ensymes: Units of Biological Structure and Function. Henry Ford Hospital International Symposium. Edited by Oliver H. Gaebler, Head, Biochemistry Department, Edsel B. Ford Institute for Medical Research, Detroit. 624 pages; 23.5 × 15.5 cm. 1956. Academic Press, Inc., New York. Price, \$12.00.
- A Follow-Up Study of War Neuroses. VA Medical Monograph. By NORMAN Q. BRILL, M.D., Professor of Psychiatry and Superintendent and Medical Director, The Neuropsychiatric Institute, University of California School of Medicine, Los Angeles, California; and GILBERT W. BEEBE, Ph.D., Statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D. C. 393 pages; 23.5 × 15.5 cm. 1956. Government Printing Office, Washington, D. C. Price, \$2.25.
- Klinische Funktionsdiagnostik. By Doz. Dr. Heinrich Küchmeister; unter mitarbeit von Prof. Dr. W. Bolt, Köln; Prof. Dr. H. Goldeck, Hamburg; and Dr. H. Hamm, Hamburg; mit einem geleitwort von Prof. Dr. A. Jores, Hamburg. 411 pages; 24.5 × 18 cm. 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 49.50.
- Kohlenhydratstoffwechsel Insulin und Diabetes. By Prof. Dr. Hans Staub. 48 pages; 23.5 × 15.5 cm. (paper-bound). 1956. Georg Thieme Verlag, Stuttgart;

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- in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 9.60.
- The Lung as a Mirror of Systemic Disease. By ELI H. RUBIN, M.D., Professor of Clinical Medicine, Albert Einstein College of Medicine, Yeshiva University, etc. 288 pages; 29 × 22 cm. 1956. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$12.50.
- The Lung: Clinical Physiology and Pulmonary Function Tests (Based on the 1954 Beaumont Lecture). By Julius H. Comroe, Jr., M.D., Professor of Physiology and Pharmacology; Robert E. Forster, II, M.D., Associate Professor of Physiology and Lowell M. Palmer Senior Fellow; Arthur B. Dubois, M.D., Associate Professor of Physiology and Established Investigator, American Heart Association; William A. Briscoe, M.D., Associate in Physiology; and Elizabeth Carlsen, A.B., Isaac Ott Fellow and Instructor in Physiology, Graduate School of Medicine, University of Pennsylvania. 219 pages; 23.5 × 15.5 cm. 1955. The Year Book Publishers, Inc., Chicago. Price, \$5.50.
- The Medical Department: Hospitalization and Evacuation, Zone of Interior. United States Army in World War II: The Technical Services. 503 pages; 25.5 × 17.5 cm. 1956. Office of the Chief of Military History, Department of the Army, Washington 25, D. C. Price, \$4.00.
- Metabolism and Function of Iron: Report of the Nineteenth Ross Pediatric Research Conference. 96 pages; 23 × 15 cm. (paper-bound). 1956. Issued by Ross Laboratories (formerly M & R Laboratories), Columbus, Ohio. Price available on request.
- Neuropharmacology: Transactions of the Second Conference, May 25, 26 and 27, 1955, Princeton, N. J. Edited by Harold A. Abramson, M.D., Research Psychiatrist, Biological Laboratory, Cold Spring Harbor, N. Y., etc. 328 pages; 23.5 × 16 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$4.25.
- Polysaccharides in Biology: Transactions of the First Conference, April 27, 28 and 29, 1955, Princeton, N. J. Edited by Georg F. Springer, M.D., William Pepper Laboratory of Clinical Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. 271 pages; 23.5 × 16 cm. 1956. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$5.00.
- Praktische Gastroenterologie. By Dr. Ernst Hafter, Zürich; mit beiträgen von Priv.-Doz. Dr. H. W. Hotz, Luzern; and Priv.-Doz. Dr. F. Deucher, Zürich. 380 pages; 24.5 × 17.5 cm. 1956. Georg Thieme Verlag, Stuttgart; available in U. S. A. from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 48.-
- Psychiatry, The Press and The Public: Problems in Communication. Editorial Board: Wilfred Bloomberg, M.D., Chairman; Louis Lyons, L.H.D., Robert T. Morse, M.D., Robert L. Robinson and Arthur Snider; Editorial Consultant: Stalla Bloch Hanau. 80 pages; 21.5 × 14 cm. (paper-bound). 1956. American Psychiatric Association, Washington. Price, \$1.00.
- Trace Elements in Human and Animal Nutrition. By E. J. Underwood, Institute of Agriculture, University of Western Australia, Nedlands, Western Australia. 430 pages; 23.5 × 15.5 cm. 1956. Academic Press, Inc., New York. Price, \$9.50.

Die Zentralnervöse Regulation des Blutbildes. By Professor Etsuzo Komiya; mit einem Vorwort von Prof. Dr., Dr. h. c. L. Heilmeyer. 72 pages; 24 × 17 cm. (paper-bound). 1956. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 12.-

COLLEGE NEWS NOTES

New Life Members

The College acknowledges with pleasure the following Fellow as a Life Member: Dr. A. Lee Edgar, San Diego, Calif.

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College expresses its appreciation to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

Col. Augustus A. Hall, M.D., F.A.C.P., Fort Bliss, Texas, "Diagnostic Biliary Drainage—A Practical Handbook for Physicians and Technicians," 1st Edition published by the Author.

Coyne H. Campbell, M.D., F.A.C.P., Oklahoma City, Okla., "A Bulletin of Neuropsychiatry," Published by The Coyne Campbell-Sleeper Clinic, edited by Patrick S. Nagle, M.D.

Dr. Leroy E. Burney, F.A.C.P., Becomes New Surgeon General of the U. S. Public Health Service

Announcement has been made of the appointment of Dr. Leroy E. Burney, F.A.C.P., formerly Health Commissioner of Indiana, but more recently Assistant Surgeon General, and Deputy Chief of the Bureau of State Services, U. S. Public Health Service. Dr. Burney succeeds Dr. Leonard A. Scheele, who resigned at the end of July, to become President of Warner-Chilcott Laboratories, Inc., Morris Plains, N. I.

Dr. Burney received his medical degree from Indiana University School of Medicine in 1930. His special interests have included accident prevention, chronic diseases and the problems of the aged. He has been a Fellow of the American College of Physicians since 1947.

POSTGRADUATE EXPENDITURES DEDUCTIBLE

The United States Internal Revenue Service permits physicians to deduct their expenditures in taking "refresher" postgraduate courses. While this ruling was established for the American College of Physicians some years back, an official regulation was adopted August 9, 1956, providing that expenditures for education are deductible if they are for a "refresher" or similar type of course taken to maintain the skills directly and immediately required by the physician in his employment or business. An educational course to be covered should be designed for established medical practitioners to help them keep abreast of current developments in the profession. Education designed to prepare the practitioner to enter a specialty is not acceptable. Not only may the tuition fee for these refresher courses be deducted, but also the expenditures for travel, meals, and lodging while away from home are deductible, but the physician may not include expenses for personal activities.

SCHEDULE OF A.C.P. REGIONAL MEETINGS, 1956

	Official Guest	E. R. Loveland, Executive Secretary	Karver L. Puestow, M.D., Regent	Wallace M. Yater, M.D.,	William B. Bean, M.D. Richard A. Kern, M.D., President-Elect	Robert Wilson, M.D., Regent		Walter L. Palmer, M.D., President E. R. Loveland, Executive Secretary	
DNAL MEETINGS, 1956	Governor and/or Chairman	Elbridge E. Johnston, M. D., Chairman Richard S. Hawkes, M.D. John C. Leonard, M.D. Richard P. Stetson, M.D. Sven M. Gundersen, M.D. Marshall N. Fulton, M.D. Clyde W. Holland, M.D. Walter de M. Scriver, M.D.	Paul J. Breslich, M.D., Chairman R. O. Goehl, M.D.	Paul H. Revercomb, M.D.	Robert Friedenberg, M.D. John H. Talbott, M.D. Richard T. Beebe, M.D., Chairman	William C. Blake, M.D., Chairman D. O. Wright, M.D. Carter Smith, M.D. Orlando B. Mayer, M.D. Carlos F. Cardenas, M.D.	Bert F. Keltz, M.D., Chairman Iohn N. Compton. M.D.	Wesley W. Spink, M.D., Chairman Frederick W. Madison, M.D. C. H. Drenckhahn, M. D. Howard W. Wakefield, M.D.	Willis M. Fowler, M.D.
SCHEDULE OF A.C.P. KEGIONAL MEETINGS, 1956	Territory	New England States & Provinces of Eastern Canada (Maine, Vt., N. H., Mass., Conn., R. I., Que. & Atlantic Provinces)	North Dakota	West Virginia	New Mexico Western New York	Southeastern (Ala., Ga., S. C., Fla., Cuba)	Arkansas-Oklahoma	Midwest (Minn., Wis., Iowa, III., Ind.)	
	City	Burlington, Vt.	Minot	Charleston	Albuquerque Albany	Nassau, Bahama Is.	Tulsa, Okla.	Minneapolis, Minn.	
	Date	Sept. 7-8	Sept. 8	Sept. 29	Oct. 16 Oct. 19	Oct. 20-21	Oct. 20	Oct. 27	

SCHEDULE OF A.C.P. REGIONAL MEETINGS, 1956-Continued

M.D.,	M.D.,	M.D.,	M.D.,	M.D.,	M.D.,	M.D.,	M.D.,	M.D.,
Official Guest Walter L. Palmer, M.D., President	Chester M. Jones, M.D., 1st Vice President Walter L. Palmer, M.D., President	Walter L. Palmer, M.D., President	Richard A. Kern, President-Elect	Richard A. Kern, M.D., President-Elect	Walter L. Palmer, M.D., President	Howard P. Lewis, Regent	Richard A. Kern, President-Elect	Richard A. Kern, President-Elect
Governor and/or Chairman Edward C. Klein, Jr., M. D. Harrold Murray, M.D., Chairman Harold W. Gregg, M.D.	H. Marvin Pollard, M.D. Elbert L. Persons, M.D. James M. Alexander, M.D., Chairman	Rudolph H. Kampmeier, M.D., Chairman Sam A. Overstreet, M.D.	Thomas M. McMillan, M.D. C. F. Kemper, M.D. C. Wesley Eisele, M.D., Chairman	Lemuel C. McGee, M.D. Ward W. Briggs, M.D., Chairman	Carl V. Moore, M.D.	George C. Griffith, M.D. Harry E. Henderson, M.D. Chairman	Charles M. Caravati, M.D.	William C. Menninger, M.D. Samuel Zelman, M.D., Chairman
Territory New Jersey Montana-Wyoming	Michigan North Carolina	Kentucky-Tennessee	Eastern Pennsylvania Colorado	Delaware	Missouri	Southern California	Virginia	Kansas
City Newark Great Falls, Mont.	Ann Arbor Chapel Hill	Nashville, Tenn.	Philadelphia Colorado Springs	Wilmington	St. Louis	Santa Barbara	Williamsburg	Topeka
Date Nov. 7 Nov. 16-17	Dec. 1 Dec. 6	Dec. 8	Jan. 18–19	Feb. 9	Feb. 23	Feb. 23-24	Mar. 2	Mar. 15

CANCER CHEMOTHERAPY BIBLIOGRAPHY

At the request of the Committee on Chemotherapy of the National Advisory Council and the National Cancer Institute, and with the advice of a committee of consultants, the Armed Forces Medical Library has compiled a bibliography of 3,700 items on the chemotherapy of cancer. This bibliography was designed to bring up to date the previous list of Dr. Helen H. Dyer (An Index to Tumor Chemotherapy, 1949); started in November of 1954, its compilation required approximately six man-years.

The bibliography is arranged by subjects, with cross references and an author index in the style of the previous bibliographies prepared by AFML and will be published as a special supplement to Cancer Research. It is partially annotated and some abstracts of foreign articles are provided. 7,800 references had to be examined in order to cull the final 3,700 items used.

Copies of the bibliography will be available for distribution in December; requests should be directed to the Cancer Chemotherapy National Service Center, Bethesda 14, Maryland.

SIXTY-THIRD ANNUAL CONVENTION OF THE ASSOCIATION OF MILITARY SURGEONS

The expanding horizons of Military Medicine will be the theme of the Annual Meeting of the Association of Military Surgeons of the United States, according to its President, Rear Adm. Winfred P. Dana, (MC), USN, F.A.C.P. The meeting will be held at the Statler Hotel, Washington, D. C., Nov. 12–14, and will point out the growing responsibilities of medicine and its associated disciplines in the Federal medical services. The Sessions will cover a broad range of subjects having military medical significance. Representative of those planned are: rapid extracorporeal oxygenation of banked blood, military operations in radiologically contaminated areas, cold weather survival, results of early studies of sleep deprivation, radiation control problems aboard nuclear submarines, and the tranquilizing drugs.

There is no charge for registration and all those interested are invited to attend.

SENIOR RESEARCH FELLOWSHIP PROGRAM ESTABLISHED

The Public Health Service of the U. S. Department of Health, Education and Welfare has established a Senior Research Fellowship Program to be administered by the National Institutes of Health of the Public Health Service. During the first year of operation the program will provide for a total of 40 to 50 awards to the Nation's medical, dental and public health schools. These awards will be increased by a like number each year for five years, until a total of 200 to 250 fellowships are awarded annually. The awards will be for a maximum of \$10,000 a year and may be retained for as long as five years. The program is designed to attract and hold able investigators in the preclinical sciences and only three applications may be made per year by each school.

Requests for information concerning this program should be addressed to the Chief, Research Fellowship Program, Division of Research Grants, National Institutes of Health, Bethesda 14, Md.

ACCP 1957 Essay Contest

The American College of Chest Physicians at its recent Annual Meeting announced increased cash awards for the 1957 essay contest on the recommendation of their Council on Undergraduate Medical Education. The Contest is open to

undergraduate medical students for the best contributions prepared on any phase in the diagnosis and treatment of chest diseases (heart and/or lungs).

The first prize will be \$500; second, \$300; and the third, \$200. Each winner will also receive a certificate of merit. The winners will be announced at the 23rd Annual Meeting of the American College of Chest Physicians to be held at New York City, May 29-June 2, 1957.

Information as to application forms and conditions that must be observed may be obtained by writing to the Executive Director, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Northwestern University Receives Grant from John & Mary Markle Foundation

Dr. Richard H. Young, F.A.C.P., Dean and Professor of Medicine, Northwestern University Medical School, has announced the receipt of a \$75,000 grant from the John and Mary Markle Foundation, for the study of a program to combine premedical and medical education. This will be used in addition to a portion of the recent \$300,000 grant from the Commonwealth Fund.

Dr. Young said "the new teaching plan would be designed to provide one continuous program of education in basic sciences, humanities and medicine. Such a program would reverse many of today's principles of teaching medicine."

Instead of two separate, sharply divided programs of undergraduate, premedical study, followed by professional study of medicine in medical school, students would begin the new course upon graduation from high school and finish with the degree of Doctor of Medicine.

The Markle Foundation Grant is for three years and the study will be conducted jointly by faculty members of the medical school, the college of liberal arts and the graduate school.

AMERICAN HEART ASSOCIATION ANNOUNCES NEW GRANTS-IN-AID

Dr. Irvine H. Page, F.A.C.P., Professor of Medicine, Frank E. Bunts Educational Institute and Director of Research, Cleveland Clinic Foundation, and President of the American Heart Association, has announced the awarding of grants-in-aid totaling \$1,042,817.36 to 180 scientists engaged in research throughout the Nation in the field of cardiovascular diseases. The new grants raised to approximately \$1,873,000.00 the sums allocated by the Heart Association to support scientific research during the fiscal year ending June 30, 1957.

Dr. Page stated that with the awarding of these new grants the Association has channeled more than \$15,250,000.00, into support of scientific research since it became a national voluntary health agency in 1948.

The nature of the awards is to help cover the costs of laboratory equipment, supplies and technical assistance for experienced investigators working on a wide variety of approved projects. Almost every field of biological investigation is represented in the list of approved projects. Many fall into the category of basic research—studies seeking to add to the general store of scientific knowledge concerning the way the heart and blood vessels function in health and disease. Among these are a number concerned with tracing the metabolic pathways of the heart muscle, the biochemical steps whereby food and oxygen are transferred into energy to be expended in the beating of the heart or stored for use in such functions as tissue growth or repair.

The new grants also provide for extensive study into the nature of arteriosclerosis, rheumatic fever, including possible hereditary factors in individual susceptibility to rheumatic fever, and also in the field of heart surgery and the grafting of new scientific materials in the heart.

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Pa., President-Elect of the American College of Physicians, will officially represent the College at the Annual Meeting and Convocation of the Royal College of Physicians and Surgeons of Canada, at Toronto, Oct. 26–27, 1956.

The American Goiter Association has announced their Van Meter prize award of \$300 and two honorable mentions for the best essay submitted concerning original work on problems related to the thyroid gland. The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Essays must be received by the American Goiter Association not later than January 15, 1957.

The award will be made at the Annual Meeting of the Association to be held May 28-30, 1957, at New York City. Additional information may be obtained by writing to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y.

The Program Committee of the American Psychosomatic Society is interested in receiving titles and abstracts of papers to be used on the program of their 14th Annual Meeting to be held at Atlantic City, May 4-5, 1957. Abstracts or papers must be received no later than Dec. 1, 1956. They should be submitted in sextuplicate and forwarded to the Program Committee Chairman, 551 Madison Ave., New York 22, N. Y.

Several members of the College were among those participating on the program of the 25th Annual Meeting of the American Academy of Pediatrics held Oct. 6-11, at New York City. They were: Carl C. Fischer, M.D., F.A.C.P., Professor and Head of the Division of Pediatrics, Hahnemann Medical College and Hospital of Philadelphia; Marion B. Sulzberger, M.D., F.A.C.P., Professor of Dermatology and Syphilology and Chairman of the Department, New York University College of Medicine and New York University Post-Graduate Medical School; Walsh McDermott, M.D., F.A.C.P., Livingston Farrand Professor of Public Health and Preventive Medicine, Cornell University Medical College; Robert A. Cooke, M.D., M.A.C.P., Consultant in Allergy, Roosevelt Hospital (New York City); M. Murray Peshkin, M.D., F.A.C.P., Professor of Clinical Medicine and Pediatrics (Allergy), Albert Einstein College of Medicine, Yeshiva University; James G. Kramer, M.D., F.A.C.P., Pediatrician, Children's and City Hospital and Summit County Children's Home (Akron, Ohio); and Edward Wasserman, M.D., (Associate), Clinical Instructor in Medicine, Yale University School of Medicine.

The National League for Nursing has received a grant of \$78,553 to support its efforts in improving nursing care for patients with polio and other diseases which require rehabilitation. The funds will further the work of the League in incorporating the technics of rehabilitation into the basic nursing curriculum as well as in the preparation of qualified nursing teachers.

This is the 17th annual contribution from the National Foundation for Infantile Paralysis to the work of the League and its predecessor organizations, which in the past worked closely with the League to improve nursing care of poliomyelitis patients through the promotion of orthopedic nursing as a specialty in educating nurses.

The Eighth International Congress on Radiology was held in Mexico City, the latter part of July, with a registration of about 2,000 doctors, 1,400 of whom were radiologists. Headquarters for the meeting was the National Auditorium where the technical exhibits were and the chief scientific program was given. All papers were translated, according to the methods used by United Nations, in four languages, English, Spanish, French and German. The General Electric Company, X-Ray Department, sponsored a Symphony Concert by the National Symphonic Orchestra, consisting of 90 musicians. New hotels are being built and Mexico City is increasingly interested in attracting medical conventions from the United States and elsewhere.

The Southern Medical Association has announced the establishment of its Distinguished Service Award. The Award is symbolized by a 14K gold medal, the first one of which will be awarded at the Association's Golden Anniversary Meeting at Washington, D. C., Nov. 12–15, 1956.

The Distinguished Service Award was established for the purpose of recognizing a physician-member of the Southern Medical Association for outstanding contributions to the advancement of medicine. The Award may also be bestowed for outstanding and meritorious work done in any field of medicine or its related and ancillary sciences.

Any member of the Association in good standing is eligible and any member may nominate a candidate for the Award. The nominees are evaluated by an unpublicized committee which selects three of the nominees annually and submits their names to the Council of the Southern Medical Association. The Council then elects one of the three submitted by the Committee on the Distinguished Service Award as the recipient.

The U. S. Department of Health, Education and Welfare, Public Health Service, has awarded six research grants totalling \$50,000, to Northwestern University Medical School. Two of the grants have been awarded to members of the College.

Dr. Samuel M. Feinberg, F.A.C.P., Professor of Medicine and Director of the Research Laboratory at Northwestern University Medical School, received \$13,700, to study how acute infection and other stresses produce relief of asthma and other allergies. The other recipient was Dr. E. Clinton Texter, Jr. (Associate), Associate in Medicine at Northwestern University Medical School, who received \$11,475, to study functional changes that occur in heartburn.

Dr. Robert L. Grissom, F.A.C.P., formerly Professor and Assistant Chairman, Department of Internal Medicine, has been named Professor and Chairman of the Department of Medicine at the University of Nebraska College of Medicine.

Dr. Irvine H. Page, F.A.C.P., Professor of Medicine, Frank E. Bunts Educational Institute and Director of Research, Cleveland Clinic Foundation and President of the American Heart Association, was awarded an honorary Doctor of Laws Degree by John Carroll University (Cleveland), at the University's commencement exercises.

Brigadier Gen. Otis O. Benson, Jr., (MC), USAF, F.A.C.P., has been appointed Commandant of the School of Aviation Medicine at Randolph Air Force Base, Texas. Gen. Benson, before assuming his new Command, was Director of Medical Staffing and Education in the Office of the Surgeon General of the United States Air Force.

Dr. John A. Di Fiore, (Associate), New York City, has been appointed by the Governor of New York State, the Honorable Averell Harriman, to serve as a member of the Medical Appeals Unit of the New York State Workmen's Compensation Board.

Major Gen. Silas B. Hays, F.A.C.P., Surgeon General, (MC), USA, was elected to an honorary fellowship in the American College of Chest Physicians at their Annual Convocation held at Chicago. The honor included a certificate and a plaque.

Dr. A. Benedict Schneider, Jr., (Associate), Cleveland, Ohio Clinical Instructor in Medicine, was recently advanced to Senior Clinical Instructor in Medicine at Western Reserve University School of Medicine.

The late Dr. Max Einhorn, F.A.C.P., New York, bequeathed \$650,000 to the Lenox Hill Hospital, to be used for research in the field of gastroenterology. Under the terms of Dr. Einhorn's will, research is to be carried forth with a view toward refining the methods of diagnosis and treatment developed by Dr. Einhorn. Income from the gift is also to be used for maintaining the Max and Flora Einhorn Building donated by Dr. Einhorn in 1937, which houses an auditorium and wards for patients with gastroenterological ailments.

The University of Oregon Medical School has received a \$200,000 gift from an anonymous friend of the school to be used as a Trust Fund for research. The Trust Fund is to be named in honor of Dr. Laurence Selling, F.A.C.P., who is Professor Emeritus of Medicine at the Medical School.

Dr. George G. Rowe (Associate), University of Wisconsin Medical School, will spend a year in postgraduate study and research in England, working in the laboratory of Dr. John McMichael and Dr. Malcolm Milne, Postgraduate School of London at Hammersmith Hospital. Dr. Rowe will also travel on the Continent, visiting particularly centers in Sweden.

On Sept. 1, Dr. William B. Tucker, F.A.C.P., began his new duties as Director of the Tuberculosis Service, Veterans Administration, Washington 25, D. C. He was formerly Professor of Medicine at Duke University, where he was Chief of the Pulmonary Disease Service (1954–55), and Chief of the Medical Service (1955–56), of the Veterans Administration Hospital.

Dr. Benjamin B. Wells, F.A.C.P., Director of the Department of Medicine, at Creighton University School of Medicine, Omaha, Nebraska, has accepted an appointment as of Sept. 1, 1956, as Director of Clinical Investigation at the Lynn Clinic, Detroit, Michigan.

Col. Benjamin H. Sullivan, Jr. (MC), USA, F.A.C.P., has been named Chief of the Gastroenterology Service at Walter Reed Army Hospital, Washington, D. C. Col. Sullivan has also been presented a Certificate of Achievement from the Commanding General of Letterman Army Hospital (San Francisco), in recognition of his outstanding performance of duty during the two-year tour which he has just completed.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., was honored upon his retirement from the Joint Committee of the Connecticut State Medical Society, the Connecticut State Dental Society and the Connecticut Pharmaceutical Association, and was made Honorary Chairman in recognition of his service as Chairman of this Committee for the past eight consecutive years.

Col. Joseph H. McNinch (MC), USA, (Associate), of the Personnel Division in the Office of the Surgeon General, has announced that internal medicine is the most popular specialty in the U. S. Army, with surgery rated second, according to the results of a recent semi-annual survey.

The Society of Nuclear Medicine at its Annual Convention held at Salt Lake City, elected the following officers for the ensuing year. President, Mr. N. J. Holter, Helena, Mont.; Vice President, Dr. Henry H. Turner, F.A.C.P., Oklahoma City, Okla.; Vice President-elect, Dr. Franz K. Bauer (Associate), Los Angeles, Calif.; Secretary, Dr. Robert Lackey, Denver, Colo.; Treasurer, Dr. Linden Seed, Chicago, III

The 1957 meeting will be held June 20-22, at the Skirvin Towers Hotel, Oklahoma City, Okla.

Dr. Nathaniel E. Reich, F.A.C.P., Clinical Assistant Professor of Medicine, State University of New York College of Medicine at New York City, was moderator of a panel on "Heart Function," at the International Meeting of the American College of Chest Physicians, held at Cologne, Germany, Aug. 22, 1956. He also gave a lecture entitled "The Versatility of the Carotid Sinus."

Dr. Nathan S. Kline, F.A.C.P., Research Associate in Neurology, Columbia University College of Physicians and Surgeons and Dr. Mortimer Ostow, New York, will speak on the psychological implications of tranquilizing drugs, at the Psychosomatic Forum of New York City, Oct. 30.

Dr. Robert C. Hardin, F.A.C.P., Assistant Dean and Professor of Internal Medicine, State University of Iowa College of Medicine (Iowa City), presented a paper before the American Diabetic Association, at their Annual Meeting held at Chicago, June 10. Dr. Hardin's paper was entitled "The Relative Importance of Duration and Control in the Development of Diabetic Retinopathy." He also had a scientific exhibit at the American Medical Association Convention entitled "Diabetic Retinopathy."

Dr. William B. Bean, F.A.C.P., Professor of Medicine and Head of the Department of Internal Medicine, State University of Iowa College of Medicine (Iowa City),

delivered a paper before the American College of Chest Physicians, at their Annual Meeting held June 8, at Chicago. His paper was entitled "Heart Failure." Dr. Bean also conducted a discussion on "Coronary Thrombosis" before the American Medical Association's Annual Meeting.

Dr. Howard T. Karsner, F.A.C.P., Medical Research Advisor for the Bureau of Medicine and Surgery, Navy Department, will be the first lecturer in a series to be given in honor of the famous pathologist, Dr. Carl V. Weller, F.A.C.P., Professor of Pathology and Chairman of the Department, University of Michigan Medical School. Dr. Karsner will lecture at Ann Arbor, Mich., Dec. 8, 1956.

The Michigan Pathology Society has established the Carl V. Weller lectureship in recognition of his many contributions to medical science in the fields of pathology

and clinical pathology.

Dr. William Dameshek, F.A.C.P., Professor of Clinical Medicine, Tufts College Medical School (Boston), will participate in a symposium on "Newer Developments in the Diagnosis and Management of Cancer," to be held at the City of Hope Medical Center (Duarte, Calif.), Nov. 14–17.

The Annual Meeting of the American Cancer Society will be held Oct. 29–30, at the Park Sheraton Hotel, New York City. In addition to its Annual Meeting, the American Cancer Society will sponsor a Scientific Session on the subject of endocrines and cancer. This Session is intended to be a summarization as well as a critical evaluation of the etiologic and therapeutic rôle which hormones play in neoplastic diseases.

Information as to the complete program may be procured by writing to the American Cancer Society, Professional Education Section, 521 West 57th, New York

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Dr. George H. Gehrmann, F.A.C.P., Assistant Professor of Preventive Medicine, Medical College of Virginia and former Medical Director of the E. I. duPont de Nemours Company, has been awarded the 9th Alumni Medallion for Distinguished Service to American Medicine by the State University of New York College of Medicine at New York City. Dr. Gehrmann was cited for his leadership of over 40 years in industrial medicine and for bringing about the collaboration of industry and medicine to protect and preserve the health of the American worker. He also has been credited with the establishment of the American Academy of Occupational Medicine as well as a specialty board of occupational medicine.

Dr. Israel Davidsohn, F.A.C.P., Professor of Pathology and Chairman of the Department, Chicago Medical School, received the Dr. Morris L. Parker Award at the 42nd Commencement of the Medical School. The \$500 award was granted to Dr. Davidsohn for his research in pathology, particularly as related to blood and immunology.

Dr. Joseph D. McCarthy, F.A.C.P., formerly Associate Professor of Internal Medicine, has been advanced to Professor of Internal Medicine at the University of Nebraska College of Medicine (Omaha).

Dr. Geoffrey W. Rake (Associate), Research Professor of Microbiology in Medicine, University of Pennsylvania School of Medicine and the School of Veterinary Medicine, has been appointed Scientific Director of the International Division of Olin Mathieson Chemical Corporation. In this capacity he will be responsible for all pharmaceutical, medical and veterinary research conducted outside the United States by the company's E. R. Squibb & Sons, Inc., International Division.

Dr. Robert K. Maddock, F.A.C.P., retired from the Public Health Service of the United States on April 1, 1956, and is now engaged in private practice at 1306 Colonial Ave., Norfolk 7, Va.

Dr. Bernard I. Lewis, F.A.C.P., heretofore Associate Professor of Medicine at the State University of Iowa, resigned September 1, 1956, to join the Staff of the Palo Alto Clinic at Palo Alto, Calif.

Dr. Hobart Reimann, F.A.C.P., formerly Professor of Medicine at Jefferson Medical College of Philadelphia, is presently serving as Medical Director of the Binghamton City Hospital at Binghamton, New York.

Roberto F. Escamilla, F.A.C.P., San Francisco, California, was recently promoted to Clinical Professor of Medicine at the University of California School of Medicine.

ABSTRACT

MINUTES OF THE BOARD OF REGENTS

Los Angeles, Calif.

APRIL 14, 1956

The first meeting of the Board of Regents during the 37th Annual Session of the American College of Physicians at Los Angeles, Calif. (April 16-20, 1956), was held on Saturday, April 14, 1956, 2:00 P.M., Biltmore Hotel; President George F. Strong presiding and Mr. Edward R. Loveland acting as Secretary. Those present were:

	George F. Strong	President
	Walter L. Palmer	President-Elect
	Edward L. Bortz	First Vice President
	Edward C. Reifenstein, Sr	Second Vice President
	Richard A. Kern	Secretary-General
	William D. Stroud	Treasurer
	Fuller B. Bailey	
	Philip S. Hench	
	Chester S. Keefer	
	T. Grier Miller	
	J. Murray Kinsman	
	Wann Langston	
	Asa L. Lincoln	
	Karver L. Puestow	
	Wallace M. Yater	
	Herbert K. Detweiler	
	Howard P. Lewis	
	Joseph D. McCarthy	
	Cyrus C. Sturgis	
	Dwight L. Wilbur	
	Maurice C. Pincoffs	Editor, Annals of Internal Medicine
		Chairman, Board of Governors
	Samuel G. Taylor, III	ACP representative on the Cancer Committee of the ACS
	Alex. M. Burgess	re meeting of AMA Stover Committee
	C. Wesley Eisele	Commission on Professional and Hospital Activities and ACP representative on the Medical Audit Committee of the ACS
	George Morris Piersol	Chairman, Committee on Credentials
	William C. Chaney	Chairman, Committee on Voluntary Pre- paid Health Insurance
	George C. Griffith	General Chairman, 37th Annual Session
ho	se absent were:	
	Leland Hawkins	Third Vice President
	Eugene B. Ferris	

Communications:

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President George F. Strong made a detailed report on his official trip to Hawaii, Australia and New Zealand, on behalf of the American College of Physicians, to attend the Hawaiian Regional Meeting of the College, to attend the Annual Session of the Royal Australasian College of Physicians and to confer with Officers and Fel-

lows of that College. At the Convocation, Dr. Strong was the recipient of an Honorary Fellowship. Dr. Strong's closing remarks on the trip were: "In view of the obvious desirability of continuing to maintain and improve good relations between all Colleges of Physicians, particularly those in the English speaking countries, such visits probably should be continued. As between the American and the Australasian Colleges, it might be appropriate to arrange for the President of each College to visit the other at the time of the Annual Meeting on alternate years. We can look forward to the visit in Boston in 1957 of the present President of the Royal Australasian College, Dr. E. G. Sayers of Auckland, the first New Zealander to occupy that position."

President Strong reported that Dr. A. B. Brower had resigned as Chairman of the Committee on Finance, and that Dr. Herbert K. Detweiler, a member of that Committee, had been appointed by the President as Chairman.

Dr. Joseph M. Hayman, F.A.C.P., represented the American College of Physicians at the First Academic Convocation of Tufts University, Boston, December 8, 1055

Dr. Willis M. Fowler, F.A.C.P., was reappointed by the Executive Committee of the College for a term of three years, from December 31, 1955, to December 31, 1958, as an ACP Commissioner on the Joint Commission on Accreditation of Hospitals.

Dr. Samuel G. Taylor, III, F.A.C.P., Chicago, ACP representative on the Cancer Committee of the American College of Surgeons, made a report on his observations of the activities of the Committee on Cancer of the American College of Surgeons. Concluding his report, he said:

"I also felt for some time that the American College of Physicians and internists in general have not been adequately active in the field of cancer therapy, with the result that most developments in palliation and disseminated cancer have been accomplished by surgeons, roentgenologists and pathologists. As an example, Ira Nathanson, Frank Adair in Steroids, Sidney Farber in Leukemia. It is interesting also that a surgeon has been chosen to head the National Chemotherapy Cancer Committee, Dr. Isadore Ravdin. The function of the interest in most tumor clinics has been passing judgment on diagnosis and operability of patients. The surgeon and the roentgenologist undoubtedly use more steroid hormones and chemotherapeutic agents in the treatment of cancer than does the internist and frequently with little knowledge of the physiological action of these drugs.

"It seems timely that the American College of Physicians enter into the cancer program more actively. This could be done by establishing a Committee on Cancer,

whose functions would be:

"1. Advising on postgraduate courses in cancer therapy.

"2. Advising on programs in regional and national meetings to disseminate knowledge of cancer therapy.

"3. Encourage more internists into going into the field of medical oncology."4. Act as a liaison between the American College of Physicians and other organizations in the field of cancer.

"This Committee could be chosen or appointed by the Regents from Fellows interested in this field. It might be advantageous to us to have members on the Committee from other specialties, such as roentgenology and surgery in somewhat the same way that the Committee on Cancer of the American College of Surgeons is set up."

On the recommendation of Dr. Walter L. Palmer, a resolution was adopted, providing that a Committee on Cancer of the American College of Physicians shall be appointed by the President, to study the part the American College of Physicians should play in the whole general problem of cancer therapy, to look into all of these

matters having to do with the relationship between the internist and the problems of cancer.

Dr. William D. Stroud, ACP representative on the Council on Rheumatic Fever and Congenital Heart Disease, made a brief report on the activities of that Council, on behalf of himself and the other ACP representative, Dr. Currier McEwen.

Dr. Stroud, as Chairman of the House Committee, also reported to the Regents that the program of improvements and replacements to the College Headquarters, authorized by the Board at its preceding meeting, November, 1955, were progressing well toward completion.

By resolution an additional regulation to those governing the Residency Revolving Loan Fund, namely, "loans will be restricted to citizens of the United States, its dependencies and Canada," was adopted. It was recorded that the capital of the loan fund had reached \$40,000.00 and that loans had been approved totaling \$13,700.00, with some applications pending.

Dr. Alex. M. Burgess, Sr., ACP Commissioner on the Joint Commission on Accreditation of Hospitals, made a brief report on the meeting of the Stover Committee of the American Medical Association, in connection with its investigation of the work of the Joint Commission.

The Secretary-General recorded the deaths of 40 Fellows and 1 Associate since the last meeting of the Board of Regents, and the names and date of death were incorporated in the Minutes. He also recorded the names of 60 additional Life Members, added since the last meeting of the Board, making a grand total of 1,388, of whom 162 are deceased, leaving a balance of 1,226.

Dr. C. Wesley Eisele, ACP Commissioner, Commission on Professional and Hospital Activities, reported that the new Commission was well established and in operation from headquarters in Ann Arbor, that Executive Officers of the American College of Physicians, American College of Surgeons, the American Hospital Association and the American Medical Association were directing an Educational Trust, through which the W. K. Kellogg Foundation would transmit a grant of some \$260,000.00 in support of the Commission. Dr. Vergil N. Slee, an Associate of the College, is directing the work of the Commission, and he and a representative of the American College of Surgeons had prepared an exhibit depicting the work of the Commission and the work of the Medical Audit Committee of the American College of Surgeons at the Annual Session of the American College of Physicians.

Dr. Eisele, also ACP representative on the Medical Audit Committee of the American College of Surgeons, stated that that Committee, in devising the medical audit, had worked closely with the medical activity of the new Commission. The audit system which had been devised had been in operation in twenty hospitals, and the audit committees in these hospitals had audited or reviewed some six thousand clinical records. In addition to auditing, the hospitals have simultaneously reviewed records on four subjects, gall bladder diseases, respiratory diseases in children, breast surgery and artery diseases. The audit forms have been revised toward greater simplification of the basic data. Special audit forms for various diseases, conditions and operations will be developed gradually.

Dr. George Morris Piersol, Chairman of the Committee on Credentials, presented a report of that Committee. 303 proposals for Associateship and 183 proposals for Fellowship had been reviewed since the last meeting of the Board, and the Committee recommended for election to Associateship 259 candidates and for election to Fellowship 131 candidates. By formal resolution the election of all recommended candidates was made by the Board of Regents (names of these candidates were published in a previous issue of this journal).

The Committee on Credentials had investigated the matter of "Service Membership" in the American Medical Association for medical officers in the Public Services, namely, the Air Force, the Army, the Navy, the Public Health Service and the

Veterans Administration. It was determined that Service Membership is available to all medical officers in these Services, and, therefore, the Committee on Credentials unanimously agreed that all members of the Government Services can and shall fulfill the requirement of AMA Service Membership before election to the College.

Dr. Asa L. Lincoln, Chairman, presented the report of the Committee on Public Relations. Growing out of the recommendations of that Committee, the Regents by formal resolutions took the following actions:

Declined with thanks the invitation of the Cincinnati Health Museum, Centennial Exposition, to set up an exhibit in Cincinnati; approved in principle the recommendation from the National Committee for a Commission on Nursing Services, that a committee of doctors, nurses, hospital administrators, and others directly concerned, be set up to study the general nursing problem; the dues of four members were waived, because of incapacitation, until such time as they are able to resume remunerative medical work; the resignations of two Associates and one Fellow were accepted.

A resolution was adopted extending permission to Audio-Digest to interview speakers on the General Sessions program, and to record their comments on subjects other than their official College lectures; like permission to Ciba Products to record certain Panel Discussions on the Annual Session program, if written permission were obtained from all members of the Panel.

Action on a report submitted by the Committee on Voluntary Prepaid Health Insurance was deferred, pending outcome of a project to set up an American Society of Internal Medicine, whose chief activity would be concerned with the subject of prepaid insurance fees and other economic problems.

Dr. Herbert K. Detweiler, Chairman, presented an extended report on the finances of the College (said report having been published already in the July, 1956, Issue of this journal).

Growing out of the Finance Committee's report, the following resolutions were adopted:

RESOLVED, it shall be the policy of the College to funnel all matters involving expenditures through the Finance Committee for analysis and study, so that the Committee may intelligently present recommendations to the Board of Regents;

RESOLVED, that the President-Elect of the College shall be granted the same expense privileges as the President when on official College business, namely, he shall receive travel expenses, plus \$50.00 per diem;

RESOLVED, that the Governors of the College shall receive round trip, first class, transportation expenses when attending the Annual Sessions of the College, and RESOLVED, that the Regents appropriate the necessary funds, up to \$7,000.00,

for the current year;

RESOLVED, that no change be made in the present travel allowances for members of the Board of Regents (round trip transportation) when in attendance at the Annual Sessions of the College;

RESOLVED, that the representative of the American College of Physicians on the Advisory Committee of the Joint Commission on Accreditation of Hospitals shall receive an honorarium of \$25.00 per diem for attendance at meetings of that Committee;

It was recommended that expenditures for foreign guests to appear on the Amual Session program be kept within the general limits of the past three or four years; RESOLVED, that the College shall provide Blue Cross and Blue Shield coverage for each of its permanent full-time employees.

Adjournment.

Attest: E. R. LOVELAND

Secretary

ABSTRACT

MINUTES OF THE BOARD OF GOVERNORS

Los Angeles, Calif.

APRIL 15, 1956

The Board of Governors met at the Biltmore Hotel, Los Angeles, Calif., Sunday, April 15, 1956; Dr. Carter Smith, Chairman, presiding, and Mr. E. R. Loveland acting as Secretary.

The following Governors and Alternate Governors were in attendance:

*Oliver C. Melson, Little Rock ARKANSAS

Stacy R. Mettier, San Francisco CALIFORNIA (Northern) and NEVADA

Willis M. Fowler, Iowa City IOWA

Marion D. Hargrove, Shreveport ... LOUISIANA
H. Marvin Pollard, Ann Arbor ... MICHIGAN
Wesley W. Spink, Minneapolis ... MINNESOTA
Carl V. Moore, St. Louis ... MISSOURI

Sven M. Gundersen, Hanover NEW HAMPSHIRE Edward C. Klein, Jr., South Orange .. NEW JERSEY Elbert L. Persons, Durham NORTH CAROLINA Robert B. Radl, Bismarck NORTH DAKOTA

*Alex. M. Burgess, Sr., Providence .. RHODE ISLAND Robert Wilson, Charleston SOUTH CAROLINA

Ellsworth L. Amidon, Burlington VERMONT
Charles M. Caravati, Richmond VIRGINIA
George H. Anderson, Spokane WASHINGTON
*M. L. Bonar, Charleston WEST VIRGINIA

Walter de M. Scriver, Montreal QUEBEC Jose J. Centurion, Havana CUBA

D. O. Wright, Birmingham ... ALABAMA
Leslie R. Kober, Phoenix ... ARIZONA
Lemuel C. McGee, Wilmington ... DELAWARE
William C. Blake, Tampa ... FLORIDA
Carter Smith, Atlanta ... GEORGIA

Richard P. Howard, Pocatello IDAHO Howard Wakefield, Chicago ILLINOIS (Northern)

Sam A. Overstreet, Louisville KENTUCKY Richard S. Hawkes, Portland MAINE R. Carmichael Tilghman, Baltimore . MARYLAND Laurance J. Clark, Sr., Vicksburg ... MISSISSIPPI

Harold W. Gregg, Butte MONTANA and WYOMING

Robert Friedenberg, Albuquerque ... NEW MEXICO

Irving S. Wright, New York NEW YORK (Eastern)

*M. A. Blankenhorn, Cincinnati ... OHIO

Merl L. Margason, Portland ... OREGON

*Alfred W. Harris, Dallas ... TEXAS

Frederick W. Madison, Milwaukee ... WISCONSIN

Percy H. Sprague, Edmonton ... ALBERTA

Charles H. A. Walton, Winnipeg MANITOBA and SASKATCHEWAN

^{*} Alternate.

George C. Griffith, Los Angeles	CALIFORNIA (Southern)
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*W.	Bernard	Yegge,	Denver	 COLORADO
Loh	n C Leon	nard Has	rtford	CONNECTICITY

Charles F. Morsman, Hot Springs	
Rudolph H. Kampmeier, Nashville	TENNESSEE
Theodore C Rayerlein Salt Lake City	ITAH

*K. J.	R. Wight	man, To	ronto	 ONTARIO
Ignacio	Chavez,	Mexico	City	 MEXICO

*O. O. Benson,	Jr	United	States	Air Force
*F. H. Mowrey	******************	United	States	Army
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Chairman Smith introduced Dr. George F. Strong, President of the College, who addressed the Board at some length concerning the pending program, concerning his trip to Australia and New Zealand for the College and concerning the responsibility of the College in medico-economic problems. Dr. Strong expressed the opinion that economics is not primarily the field of activity for the College, and suggested the possibility that the newly developing state societies of internal medicine might readily pursue the whole problem of economics.

Chairman Smith announced the proceedings of the newly created Executive Committee of the Board of Governors, which met in Philadelphia, November 12, 1955. An Executive Committee of the Board of Governors had been deemed advisable, the Committee to meet in November and prior to the Annual Sessions in April each year; a nine-member Committee, the Chairman of the Board of Governors to be the Presiding Officer, the immediate past Chairman of the Board to be a member for one year and the Vice Chairman of the Board to be an ex officio member, with voting privilege during his term of office; the personnel of the Committee, as appointed by the Chairman:

Governors' Executive Committee
Carter Smith, Atlanta, Ga., Chairman
Theodore C. Bauerlein, Salt Lake City, Utah
Charles M. Caravati, Richmond, Va.
Charles A. Doan, Columbus, Ohio
George C. Griffith, Los Angeles, Calif.
William C. Menninger, Topeka, Kans.
William S. Middleton, Washington, D. C.
Richard P. Stetson, Boston, Mass.

Irving S. Wright, New York, N. Y.

^{*}Eli R. Movitt Veterans Administration

^{*} Alternate.

Dr. Smith reported on the following points that were considered:

- (1) The relation of the College to other organized internist groups—The Committee recommended that the College not participate in any movement to unite with groups of internists in any organization not within the present aims and policies of the College. Some of these groups were considered more socio-economic than the College, and less educational and scientific. Dr. Bauerlein was appointed to form and act as Chairman of a Committee to study on a nationwide basis such other organizations, and to report at the Los Angeles Session;
- (2) Means of intercommunication between Governors—Recommended that Minutes of the Executive Committee meetings be sent to all the Governors, with request for comments or suggestions;
- (3) Criteria for elevation to Fellowship—Recommended that a candidate for advancement to Fellowship shall have a choice of submitting (a) an adequate number of acceptable publications; (b) a clinical thesis; (c) a clinical report on five of his most interesting cases, worked up in a detailed fashion, the cases to be selected from his practice since he became an Associate. Such a report shall include not only the clinical report, but also laboratory reports, x-ray findings and all other pertinent data, with a review of the literature, discussion of the medical subject involved, and a bibliography;
- (4) Term of office of ACP Governors—Recommended that the term of office be limited to two terms of three years each; completion of an unexpired term to which the Governor may have served by appointment should not be considered a part of the regularly elected two terms of three years;
- (5) Duration of Associateship—No change recommended in the present ten-year term; recommended that Board certification be a requirement for Associateship:
- (6) Governors-Elect—Recommended that the Board of Regents consider amendments to the By-Laws, providing that Governors be elected one year in advance of taking office, such Governors-Elect to attend and participate in the meetings of the Board of Governors.

Dr. Richard P. Stetson then reported on an early morning meeting, on April 15, of the Executive Committee, with Doctors Smith, Menninger, Bauerlein, Caravati, Wright, Strong and Stetson present. The Committee at this meeting had reconsidered the points presented at the November meeting of the Committee. The Governor for Eastern New York had essentially applied, on a trial basis, the requirement of certification prior to his endorsing candidates for Associateship, and in his opinion it had met with the entire coöperation of the membership. A report had been received from Dr. Bauerlein on a trial survey of his special committee, whose purpose it had been to determine the attitude of physicians throughout the United States toward the College. Governors had been urged to use the Executive Committee as an instrument whereby they may bring to the Board of Governors problems and proposals for more intelligent discussion.

Dr. Bauerlein then reported for his special committee, saying its aim is to determine the attitude of internists in the United States toward the American College of Physicians, that the committee members had been selected from different parts of the country, in order to get a sampling of the points of view in the various territories. Form letters in a pilot study were sent to qualified internists who are non-members of the College and to Associates, including two groups, clinical and academic. The letter emphasized this is in no sense solicitation of membership, but

simply an attempt at self appraisal. The survey, thus far, had been on a small scale, but it was intended to be expanded further. Results obtained thus far had been tabulated and had served to stimulate further studies in other parts of the country. The questionnaire contained the following questions:

(1) Do you, as a non-member or as an Associate, intend to join the American College of Physicians or advance your status in the College?

(2) Do you think the College, as the leading organization of internists in this country, fairly represents the point of view of our specialty?

(3) What complaint do you have to make regarding the College as it is now constituted?

About 250 questionnaires were sent out by members of the committee to individuals that they selected from their own states. Replies were tabulated; some fairly interesting, contrasting points of view were brought out. The replies were tabulated in two categories—full-time teacher internists and practicing internists, the latter being in some instances part-time teachers.

Percentage analyses were presented; findings, though inconclusive, elicited much interest and discussion.

Chairman Smith read a communication presented by Dr. Marion A. Blankenhorn, Alternate Governor for Ohio, this communication bearing the following resolutions, but on which the Committee took no official action:

"RESOLVED, that the Fellows and Associates of the American College of Physicians in Ohio, through their Governor, be cordially receptive to a local Ohio Society of Internists in matters pertaining to regional professional economics and administrative problems, as well as to the practice of Internal Medicine. In so doing, the Governor of the College can be spokesman for such internists at the state and national levels, and thus further and promote the interest of Internal Medicine."

After extended discussion, the following resolutions were adopted:

RESOLVED, that the Board of Governors should review the question, as to whether or not the American College of Physicians should take an active interest in the economic and political problems of internists;

RESOLVED, that the Bauerlein Committee of the Board of Governors, with others that may be appointed at the pleasure of the Chairman, shall take into consideration these matters in addition to their present objectives, and report their advice to the Board of Governors at the 1957 meeting.

Open Discussion:

(1) Development of state societies of internal medicine—no official connections or parallel programs exist between these societies and the American College of Physicians; they are devoted purely to social and economic activities. The College should probably abandon the idea of entering the field of economic medicine and turn that problem over to these state societies of internal medicine.

(2) Board certification for Associates—many favored present status quo, that Associateship should be a period for development and inspiration, a period when an Associate may complete certification, as well as attain other qualifications; many maintained that the College standards must be not only maintained, but increased; others expressed feeling that certification should be abandoned altogether, because it keeps out many worthy and well qualified men.

RESOLUTIONS ADOPTED

It was RESOLVED, that these questions be referred back to the Executive Committee of the Board of Governors.

RESOLVED, that the Board of Regents shall further consider fees and dues of full-time teachers and others on similar levels, in order to encourage this group of important men to become members of the College and more active participants in all the activities of the College.

RESOLVED, that the Board of Governors recommend to the Board of Regents that the Constitution and By-Laws be amended, limiting the maximum term of Governors to two successive terms of three years each.

The latter part of the meeting was devoted to general discussion of Governors' problems, such as difficulty in getting material published in the Annals of Internal Medicine, because of the popularity of the journal, and the length of time before such material is published; type of papers appearing on the Annual Session program; broadening the basis for accepted papers, including more material of a basic nature, which would attract interest of physicians who are part-time teachers, as well as regular practitioners; admission of non-members to the Annual Sessions.

Adjournment.

Attest: E. R. LOVELAND

Secretary

ABSTRACT

MINUTES OF THE JOINT EXECUTIVE SESSION OF THE

BOARD OF REGENTS AND BOARD OF GOVERNORS

Los Angeles, Calif.

APRIL 15, 1956

The annual Joint Executive Session of the Board of Regents and of the Board of Governors of the American College of Physicians was held at the Biltmore Hotel, Los Angeles, Calif., Sunday, April 15, 1956, at 2:00 P.M., presided over by George F. Strong, M.D., President, and with Mr. Edward R. Loveland acting as Secretary.

Present:

0	ficers	and	Regents:	

George F. Strong President

Walter L. Palmer President-Elect

Edward L. Bortz First Vice President

Edward C. Reifenstein, Sr. Second Vice President
Leland Hawkins Third Vice President
William D. Stroud Treasurer
Richard A. Kern Secretary-General

Fuller B. Bailey Philip S. Hench

Chester S. Keefer

T. Grier Miller

J. Murray Kinsman

Wann Langston

Asa L. Lincoln

Karver L. Puestow

Wallace M. Yater Herbert K. Detweiler Howard P. Lewis Joseph D. McCarthy

Cyrus C. Sturgis

Dwight L. Wilbur
Maurice C. Pincoffs Editor, Annals of Internal Medicine

Carter Smith Chairman, Board of Governors

Guests:

William C. Chaney Chairman, Committee on Insurance Marion A. Blankenhorn Chairman, ACP Study of Hospital Stand-

ards in Medicine

Chester M. Jones Chairman, American Board of Internal

Medicine

Governors:

*Oliver C. Melson, Little Rock ARKANSAS

Stacy R. Mettier, San Francisco ... CALIFORNIA (Northern) and NEVADA

Willis M. Fowler, Iowa City IOWA

^{*} Alternate.

Marion D. Hargrove, Shreveport	LOUISIANA
H. Marvin Pollard, Ann Arbor	MICHIGAN
Wesley W. Spink, Minneapolis	MINNESOTA
Carl V. Moore, St. Louis	MISSOURI
Sven M. Gundersen, Hanover	NEW HAMPSHIRE
Edward C. Klein, Jr., South Orange	NEW JERSEY
Elbert L. Persons, Durham	NORTH CAROLINA
Robert B. Radl, Bismarck	NORTH DAKOTA
*Alex. M. Burgess, Providence	RHODE ISLAND
Robert Wilson, Charleston	SOUTH CAROLINA
Ellsworth L. Amidon, Burlington	VERMONT
Charles M. Caravati, Richmond	VIRGINIA
George H. Anderson, Spokane	WASHINGTON
*M. L. Bonar, Charleston	WEST VIRGINIA
Walter de M. Scriver, Montreal	QUEBEC
Jose J. Centurion, Havana	CUBA

	D. O. Wright, Birmingham	ALABAMA
	Leslie R. Kober, Phoenix	ARIZONA
	Lemuel C. McGee, Wilmington	DELAWARE
	William C. Blake, Tampa	FLORIDA
	Carter Smith, Atlanta	GEORGIA
	Richard P. Howard, Pocatello	IDAHO
	Howard Wakefield, Chicago	ILLINOIS (Northern)
	Sam A. Overstreet, Louisville	KENTUCKY
	Richard S. Hawkes, Portland	MAINE
	R. Carmichael Tilghman, Baltimore	MARYLAND
	Laurance J. Clark, Sr., Vicksburg .	MISSISSIPPI
	Harold W. Gregg, Butte	MONTANA and WYOMING
	Robert Friedenberg, Albuquerque	NEW MEXICO
	Irving S. Wright, New York	NEW YORK (Eastern)
26	M. A. Blankenhorn, Cincinnati	OHIO
	Merl L. Margason, Portland	OREGON
19	Alfred W. Harris, Dallas	TEXAS
	Frederick W. Madison, Milwaukee .	WISCONSIN
	Percy H. Sprague, Edmonton	ALBERTA
	Charles H. A. Walton, Winnipeg	MANITOBA and SASKATCHEWAN

George C. Griffith, Los Angeles	CALIFORNIA (Southern)
*W. B. Yegge, Denver	COLORADO
John C. Leonard, Hartford	CONNECTICUT
John Minor, Washington	DISTRICT OF COLUMBIA
Charles H. Drenckhahn, Urbana	ILLINOIS (Southern)
James O. Ritchey, Indianapolis	
	KANSAS
Richard P. Stetson, Boston	MASSACHUSETTS
Edmond M. Walsh, Omaha	NEBRASKA
John H. Talbott, Buffalo	NEW YORK (Western)
Bert F. Keltz, Oklahoma City	OKLAHOMA
Thomas M. McMillan, Philadelphia	PENNSYLVANIA (Eastern)
*Jack D. Myers, Pittsburgh	PENNSYLVANIA (Western)
Charles F. Morsman, Hot Springs .	SOUTH DAKOTA
Rudolph H. Kampmeier, Nashville .	TENNESSEE

^{*} Alternate.

Theodore C. Bauerlein, Salt Lake

City UTAH
*H. H. Walker, Honolulu HAWAII

H. Archibald Des Brisay, Vancouver BRITISH COLUMBIA

*K. J. R. Wightman, Toronto ONTARIO Ignacio Chavez, Mexico City MEXICO

*O. O. Benson, Jr. United States Air Force *F. H. Mowrey United States Army

*I. L. V. Norman United States Navy

*Robert L. Griffith United States Public Health Service

*Eli R. Movitt Veterans Administration

President Strong introduced Dr. Lewis T. Bullock, member of the California Society of Internal Medicine, and invited him to discuss the subject of state societies of internal medicine and the developments pointing to an American Society of Internal Medicine. Dr. Bullock, before starting his discussion, introduced Dr. George Wever, President of the California Society of Internal Medicine, and Dr. Walter Beckh, F.A.C.P., a former Officer. Dr. Bullock first bespoke mutual understanding and coöperation among state societies of internal medicine, the proposed national society and the American College of Physicians. He described the work and aims of his society, which had been faced with the problem that unless some means could be found for defining specialization, orienting and presenting what they do to insurance companies in general and to the Government, that the practice of internal. medicine would necessarily disappear. They had sought recognition of internal medicine as distinguished from general practice. Insurance schemes had not adjusted fees recognizing the internists. No allowances in compensation have been made for the time in scientific study required by the internist. The program of his society had been carried on through Blue Shield, the California Medical Association, insurance companies in general, labor unions and various Government groups, attempting to define to them what is good internal medicine, to translate its meaning in the actual practice in a community and to recommend adequate compensation for such service. Another objective had been to educate the public as to what an internist is, what service he performs and his contribution to their health and welfare.

The Secretary reported that Dr. Thomas H. Brem, F.A.C.P., had been appointed to fill out the unexpired term of Dr. John S. Lawrence, an ACP representative on the American Board of Internal Medicine, to June 30, 1956.

Dr. Edward L. Bortz, Chairman of the Committee on the Martin Bequest, reported that Artist Ferruccio Panepinto had concluded a composite portrait of the late Drs. Charles F. Martin and Alfred Stengel, as an historical painting representing the most important period in the development of the College.

Dr. Walter L. Palmer, Chairman of the Editorial Board of the Annals of Internal Medicine, reported in some detail on the journal, with regard to scientific contents, elapsed interval between receipt and publication of manuscripts, advertising income, a proposal for increasing advertising rates on January 1, 1958, mechanical features of the journal, growth in circulation (currently 20,450 copies monthly, largest of any journal in its field).

Dr. William C. Chaney, Chairman, made a progress report for the Committee on Insurance. Accident and Health: members currently insured, 4,015; November, 1955, 3,913; number of claims to date, 1,156; total amount of benefits paid to date, \$584,564.00; benefits, therefore, aggregate more than a half million dollars; three members met untimely deaths by accident and their beneficiaries each received

^{*} Alternate.

\$5,000.00. The monthly total benefits paid to members is showing a gradual increase, currently amounting to about \$20,000.00 per month. This is the trend that has been anticipated.

Professional Liability: number of members currently insured, 1,917; number of claims or possible claims, 41; amount paid in settlement of claims, \$10,621.00. It is remarkable that so few malpractice claims have arisen, but that we expected, because of the superior risk represented by members of our College. Mr. Elliott, representing Lloyds of London, by letter, has reported to us his marked satisfaction with the College Plan, with the results and with the increasing number of members joining the group. He stated that the result of the group scheme reflects very favorably on the high standing of the American College of Physicians members.

Dread Diseases: members currently insured, 1,916; number of claims to date, 17; total amount of benefits paid to date, \$8,957.94. The Committee is very gratified with this result also. This insurance covers poliomyelitis, scarlet fever, tetanus, leukemia, primary encephalitis, primary meningitis, diphtheria, smallpox, rabies, tularemia and typhoid fever. The carrier now adds to this list Rocky Mountain

spotted fever and mumps in adults.

The Committee has been more than pleased with Messrs. Claypoole and Claypoole,

who are operating the Group Insurance Plans for the College.

Dr. Edward L. Bortz, Chairman of a Special Committee on Certification of Non-Medical Personnel, reported a very rapid development in the field of certifying boards in various medical specialties, and referred to certain groups of non-physicians, such as biochemists, enzymologists, technicians, clinical pathologists, and others. They are interested in developing similar boards in their fields, preferably under the aegis of the Council on Medical Specialties of the American Medical Association. He discussed the problem at length, pointing out that many physicians oppose certifying boards for non-medical personnel. While there actually exist in some instances independent certifying boards, as in the case of the American Board of Nutrition, his Committee thereupon referred this matter back to the Board of Regents for advice and decision. No sufficiently definite and clear opinions were obtained from members of the Board, and the President decreed that the subject would be passed over without action.

Dr. Marion A. Blankenhorn, Director of the ACP Study on Hospital Standards in Medicine, reported that he has been following, insofar as possble, the report and recommendations of the College Committee headed by Dr. Arthur R. Colwell. He had consulted with the Officers of the Joint Commission on Accreditation of Hospitals and the Council on Medical Education and Hospitals. He had set up a group of part-time surveyors from among seasoned internists, and had made application to the National Institutes of Health for a grant for continuation of the study. The

survey had been gotten well underway.

Dr. Chester M. Jones, Chairman, made a lengthy report on the American Board of Internal Medicine, purpose of which was to keep the Regents of the College informed. President-Elect Palmer inquired as to the size of the pool of internists who qualify for admission to Board examinations and yet who do not succeed in attaining certification. Dr. Jones estimated that about 30% of those who take the examinations never attain full certification, and this figure he said would establish some estimate when it is considered that about 1,700 physicians register for the Board examinations yearly.

It was pointed out by President Strong that the American College of Physicians was founded primarily on the principles of the Royal College of Physicians of London; that all other "Colleges" conduct their own entrance examinations, whereas the American College of Physicians utilizes the American Board of Internal Medicine

for that purpose, although passage of such examinations is only a partial requirement for Fellowship in the American College of Physicians.

Dr. Howard P. Lewis, Chairman of the Committee on Awards, proposed to the meeting that the College establish an additional award, in addition to the Phillips and Bruce Memorial Awards, this award to be a recognition for doctors of medicine and for a particular type of investigation and/or teaching that is not done by any other group of people that the College has to consider. It was suggested that the award should be a medal, with wording equivalent to that of the Phillips Award; that this award would not preclude M.D.'s from being included in consideration for the Phillips Award.

RESOLUTIONS ADOPTED

RESOLVED, that the Committee on Awards be requested to bring in specific recommendations at the November, 1956, meeting of the Regents, with respect to the form that the award shall take, the requirements governing the award, the name of the award, the type of medal and the size of the honorarium.

RESOLVED, that in accordance with the recommendations of the Committee on Masterships, the American College of Physicians shall grant an Honorary Fellowship to Dr. Macdonald Critchley, of London, England, at this Session of the College.

RESOLVED, that the Regents and Governors of the College in their joint meeting give their approval and support to the present effort to obtain a National Library of Medicine.

Dr. LeRoy H. Sloan, ACP Commissioner and Chairman of the Joint Commission on Accreditation of Hospitals, reviewed the organization of the Joint Commission, consisting of twenty Commissioners and an Advisory Committee of five. He described an appeal group, through which complaints from hospitals may come through regular channels. Such appeals may not come from numerous sources unofficially, but must come from the administrator of the hospital to the Joint Commission and then be referred to the appeal group.

Dr. Sloan reported that during the past year the Commission has altered its rules and regulations and made possible the appointment of surveyors who will operate directly under the Joint Commission, rather than entirely or partially under the participating societies, such as the American Medical Association, the American Hospital Association, the American College of Physicians.

Dr. Sloan said that the Commission was organized in part to get away from the multitude of examinations made by various bodies, and to coördinate and correlate the work from that angle. It has been attempted to have a survey cover all departments of a hospital, including building, foods, services and everything else. The Commission recognizes the weakness of this plan, but there is a financial consideration to be kept in mind. If the Joint Commission were to employ surveyors for each and every department, it would probably increase the budget so greatly that the project could not be carried out. Dr. Sloan asked patience and forebearance in the development of better operating plans.

Dr. Sloan thereupon reported on the investigation of the Joint Commission by the "Stover Committee" appointed by the American Medical Association. The Commissioners had met with the Stover Committeemen and found its members a fine group of sensible men that will come forth with a very sensible report. Dr. Sloan predicted a favorable outcome of the Stover Committee investigation and bespoke the ardent support of the College for the Joint Commission.

In discussion that followed, Dr. Sloan assured the Board that its representatives on the Commission would adequately screen surveyor appointees who will be paid

from funds supplied by the College; also that the plan is to make an appropriation to the Joint Commission for the payment of salaries of these surveyors. All surveyors must work under the direction of the Director of the Commission. All surveyors

veyors must do the same job.

The General Chairman of the Annual Session, Dr. George C. Griffith, reported that a television show, dealing with the subject of conorary disease, had been produced by three members of the College and released over Channel 11. "The Herrick Story" (Dr. James B. Herrick, M.A.C.P.) was narrated by Dr. Howard West and will appear on N.B.C., April 22, and will run for fifteen minutes. Dr. Griffith also referred to a TV presentation over Channel 2 on April 9 of the Carnation Award to the College, received by Dr. Leland Hawkins, Third Vice President of the College. It is estimated that thirty-nine million people saw the presentation of the award. Dr. Griffith then explained in some detail local plans for publicity through the press, magazines, radio and television.

Dr. Thomas M. McMillan, Chairman of the Governors' Committee on Postgraduate Courses, made an extended report on the work of that Committee and gave a tentative schedule of courses for the autumn of 1956 and the spring of 1957.

Dr. Howard P. Lewis presented and explained a questionnaire devised by the Committee on Educational Policy to evaluate the degree of satisfaction of members with the Annual Session program, the questionnaire having been distributed to every member of the College as he registered at this Annual Session.

The joint meeting adjourned, and President George F. Strong immediately

reconvened a meeting of the Board of Regents.

Dr. Howard P. Lewis, Chairman, presented copies of proposals submitted by the Committee on Educational Policy to the Board of Regents on November 12-13, 1955, the proposals being confined chiefly to ways and means of improving the program of the Annual Session. The proposal recommended the formation of a Program Committee, to assist the President in arranging the program of Morning Lectures and General Sessions, the President to be Chairman ex officio and the General Chairman of the Session to be a member ex officio. Suggestions from the Committee were as follows:

"(1) The members would hold office for approximately three years, and rotation would be maintained, so that two new members would be appointed yearly, while two would be rotated off. The size of the Committee would have to be determined. Six might be a desirable number.

"(2) A balance in its membership would be maintained between those whose main interest is in investigation and those whose interest is in clinical

medicine.

"(3) A secretary would be appointed, from among the members, whose duties would be those of maintaining the correspondence, collecting the papers, stimulating submission of papers, and preparation for the Committee meetings. The whole Committee membership would act in regard to the procurement of an adequate number of papers to insure a wide selection.

"(4) Papers would be screened by the Committee, by methods to be determined and at a whole Committee meeting in February, or some other date, final or tentative final selection of the contributions to be used would be made. The President, as Chairman, would, of course, be in close touch with all proceedings and decisions, but would be spared the burden of trying to do all this himself. He also, obviously, would have to make the decision of just what papers would be finally included.

"(5) From the papers submitted, the Committee would select those that are proper for the Morning Lectures and those that are appropriate for the

General Sessions.

"While the suggestion of a Program Committee was made with the knowledge that such a step would represent a major change and would, if adopted, require considerable study and care in its formation, the Committee, nevertheless, felt it is a

step that sooner or later must be taken.

"The Committee also believed the program booklet of the Annual Sessions should be wider and shorter, and should include short abstracts of the papers presented. Generous interleaved, blank pages for notes were felt to be highly desirable. Some system of delineating the various sections of the program by different colors of paper or by colored lines along the page margins would help the user to quickly find what he sought."

The report was discussed at great length. It was

RESOLVED, that this report of the Committee on Educational Policy be received and referred to the Consulting Committee on Annual Sessions.

RESOLUTIONS ADOPTED

RESOLVED, that the present regulation concerning election of Associates shall apply also to the election of Fellows, and that the Committee on Constitution and By-Laws shall investigate the necessity of amending the By-Laws accordingly: By-Laws, Article VII, Section 1 (c): "He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions."

RESOLVED, that two recommendations from the Executive Committee of the Board of Governors, referring to (1) maximal term of Governors and (2) a plan of Governors-Elect be referred back to that Committee for further study and consideration.

RESOLVED, that the resolution received from the Committee on Voluntary Prepaid Health Insurance, delegating authority to Governors of the College to appoint members in their respective territories to be known as a State Committee of the American College of Physicians on Prepaid Health Insurance, be permanently tabled and the Committee discharged with thanks, because of the organization of an American Society of Internal Medicine, whose prime objectives will be toward economic matters affecting the internist.

Adjournment.

Attest: E. R. LOVELAND
Secretary

ABSTRACT

MINUTES OF THE BOARD OF REGENTS

Los Angeles, Calif.

APRIL 20, 1956

A meeting of the Board of Regents was held at the Biltmore Hotel, Los Angeles, Calif., Friday, April 20, 1956, starting at 9:00 A.M., with President Walter L. Palmer presiding and with Mr. Edward R. Loveland acting as Secretary.

The following were in attendance:

Walter L. Palmer President
Richard A. Kern President-Elect

George H. Anderson Second Vice President

Fuller B. Bailey
Philip S. Hench
George F. Strong
J. Murray Kinsman
Wann Langston
Asa L. Lincoln
Karver L. Puestow
Herbert K. Detweiler
Howard P. Lewis
Joseph D. McCarthy

Cyrus C. Sturgis
Dwight L. Wilbur

Carter Smith Chairman, Board of Governors

George Morris Piersol Chairman, Committee on Technical Exhibits

This meeting was the first meeting of the newly constituted Board of Regents, and the proceedings concerned primarily administrative matters.

Invitations for the 1958 Annual Session from Atlantic City, Cleveland, New York City, Miami, Miami Beach and Minneapolis were presented by the Secretary and/or sponsors of the invitations. One invitation, St. Louis, was for the year 1959. Tentative invitations for future years were presented from Dallas and Houston.

Action of the Board was deferred until later in the meeting.

Dr. George Morris Piersol, Chairman, reporting for the Committee on Technical Exhibits, announced that that Committee had continued to supervise advertising in the Annals and to evaluate the technical exhibits. The Committee had personally inspected all of the exhibits at this Session and had evaluated them as dignified, attractive and not objectionable in most instances. However, the Committee had determined to either delete two of the exhibits or to demand a higher plane of managing their exhibit. In one instance, criticism was not with the product, but due to high pressure methods of salesmanship carried on by the representative. The Committee had observed with approval that there was a minimal amount of sampling; also that the samples on display were put up in such a position that they were not readily picked up by visitors. Many exhibitors have adopted the policy of not handing out samples, but of sending samples on request to the office of the doctor. The Committee, though not responsible for the Scientific Exhibit, had inspected them and found them extremely interesting, and many of educational value. However, the Committee pointed out that the College will have to decide whether or not at future Sessions Scientific Exhibits shall be encouraged or eliminated, and, if encouraged, a committee should be put in charge thereof. Dr. Piersol's Committee

thought they do not blend too well with the ordinary Technical Exhibits, and actually act as detractors from the Technical Exhibits in the opinion of some of the exhibitors. Dr. Piersol emphasized that the College owes the technical exhibitors appreciation and encouragement. At the end of the first day, the Committee and the Executive Secretary met with the chief representatives of the technical exhibiting firms; the meeting was well attended, beyond the capacity of the room; the Committee obtained expressions of opinion from the exhibitors and asked for suggestions. The general feeling of the exhibitors was that this College is a very satisfactory one before which to exhibit; they are treated well, and on the whole have a successful exhibit.

The Executive Secretary, Mr. Loveland, emphasized the importance of the Board of Regents establishing a policy with regard to instituting Scientific Exhibits. The previous policy had been that the College would not sponsor Scientific Exhibits, but rather recommend that the Scientific Exhibit of the American Medical Association be the national exhibit of its kind for the country. He expressed the opinion that if the College shall enter this field, sponsoring a Scientific Exhibit in Internal Medicine, it ought to do it on a broad basis, making the Scientific Exhibit an all-inclusive affair. The small Scientific Exhibit, sponsored by the medical schools of the West Coast and the Rocky Mountain States, at Los Angeles had been designated by the Regents as no precedent for future years. Mr. Loveland stated that if the College shall embark on a Scientific Exhibit program, it will be necessary to have a very active and efficient Committee on Scientific Exhibits and it might readily require a paid director, such as has the American Medical Association. He also pointed out that the establishment of a Scientific Exhibit might require certain readjustments and even the omission of General Sessions, because the average city has inadequate space available, if the present Technical Exhibit and the large General Sessions are used to occupy the areas now required.

President Palmer remarked that if the College shall have Scientific Exhibits, they must be the finest that can be assembled. He foresaw the possibility of 150 or more such exhibits within two years after the program is started and prophesied a cost of \$65,000.00 a year, involving the employment of a director and staff.

RESOLUTION ADOPTED

RESOLVED, that the general problem of Scientific Exhibits be referred to the Committee on Educational Policy, with the request that they study the matter carefully and report to the November, 1956, meeting of the Board of Regents.

There was some discussion of the matter of having the Committee on Educational Policy to include also the Postgraduate Course program, and all other educational functions of the College. It was also requested that the report of the Committee on Educational Policy be prepared and distributed to members of the Board of Regents a week or so in advance of the Regents' meeting.

The Executive Committee of the Board of Governors submitted the following recommendations from its meeting of April 18:

- (1) That the College consider a substitute plan for the Reception and Dinner to New Members on the second evening of the Annual Session, namely, that wives be included and that instead of having a cocktail party and dinner, there be an informal but fairly extensive cocktail party and smorgasbord. That would make a free evening otherwise and would still give the new members an opportunity to meet the Officers and Regents of the College.
- (2) The employment of a part-time or full-time person by the Collecto assist in the preparation and planning of the Annual Session, to lighten the entire load on the Executive Secretary, the General Chairman, the President, and possibly some committees.

After discussion of the first recommendation, and since the Board of Governors as a whole had not been consulted, Dr. Carter Smith, the Chairman of the Board of Governors, was asked to set up a questionnaire and poll the Governors with regard to (a) a change from a reception and dinner to a cocktail party and smorgasbord, and (b) to determine if Governors prefer to issue the invitations personally.

In regard to suggestion 2, opinion was expressed that this problem would be readily resolved if the Executive Secretary had at his command competent assistants in adequate number to assign one this specific duty; it was recommended to the Executive Secretary that he provide for these additional needs by further building up his staff.

RESOLUTION ADOPTED

RESOLVED, that the number of ACP representatives on the Residency Review Committee be increased to four, and that Dr. John C. Leonard, Governor for Connecticut, be added.

By regular process, according to provisions of the Constitution and By-Laws, and/or special resolutions previously adopted by the Board of Regents and/or the Board of Governors, Committee personnel was appointed or elected (Committees and their personnel have already been published in this journal).

The following Committees were discharged with thanks:

Committee on Martin Bequest

Committee to Study Certifying Boards for Non-Medical Personnel

Committee on Voluntary Prepaid Health Insurance

RESOLUTION ADOPTED

RESOLVED, that the Board of Regents approve in principle the setting up of its standing Committees, with adequate terms of reference, and then set up machinery governing special or short-term committees—this work to be done through Dr. George F. Strong, Chairman of the Committee on Constitution and By-Laws.

RESOLUTIONS ADOPTED

RESOLVED, that Atlantic City, N. J., be designated as the 1958 meeting city. RESOLVED, that the dates shall be April 28-May 2, 1958.

RESOLVED, that Dr. James F. Gleason, F.A.C.P., be appointed the General Chairman for the 1958 Session.

RESOLVED, that Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., be elected Secretary-General of the American College of Physicians.

RESOLVED, that Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., be reelected Treasurer of the American College of Physicians.

RESOLVED, that Dr. Robert Wilson, F.A.C.P., Charleston, S. C., be elected a member of the Board of Regents, to succeed Dr. Wallace M. Yater, until the next annual election, April, 1957, authorization arising from the By-Laws, Article II,

RESOLVED, that the College extend an invitation to the President of the Royal Australasian College of Physicians to come to the 1957 Boston Session, the College to pay expenses not exceeding \$3,000.00; that this invitation be issued promptly—this resolution being presented for approval in principle, at least, by the Regents.

RESOLVED, that a Committee on Fund Raising be appointed by the President, with instructions to conduct a survey of the availability of a large sum of money that may be used for the two projects heretofore discussed (to advance good inter-

national relations among physicians by bringing speakers periodically from anywhere in the world to America; to provide financial means to assist young men and young women desiring to come to America for postgraduate medical work).

Thereupon, President Palmer appointed Dr. George F. Strong, Chairman, Dr. Joseph D. McCarthy, Dr. Philip S. Hench, Dr. Cyrus C. Sturgis and Dr. J. Murray

Kinsman.

In discussing arrangements for the Annual Convocation, two suggestions were made for the purpose of shortening the meeting, though no official action was taken:

- (1) Omit the Convocational Lectureship and retain only the Presidential Address;
- (2) The publication of various citations in the program itself, and omitting reading them on the occasion of conferring special honors and awards.

The first item was deferred for further consideration by the Regents; the second item was objected to by many, who felt that the recipient of an award deserves to have his honors proclaimed, as it were, to the audience.

ANNOUNCEMENT

Autumn meetings of Committees and Board of Regents, November 9-10-11, 1956, at the College Headquarters in Philadelphia.

Adjournment.

Attest: E. R. LOVELAND
Secretary

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns,

- Dr. William Juel Bryan, Jr., F.A.C.P., Tulsa, Okla., July 4, 1956
- Dr. Elmer Highberger, Jr., F.A.C.P., Greensburg, Pa., July 28, 1956
- Dr. Walter Henry Krombein, F.A.C.P., Buffalo, N. Y., July, 1956
- Dr. Malcolm Christian McCord, Associate, Denver, Colo., July, 1956
- Dr. Philip Ingram Nash, F.A.C.P., Brooklyn, N. Y., April 25, 1956
- Dr. Nelson Gorham Russell, Sr., F.A.C.P., Buffalo, N. Y., June 4, 1956 Dr. Will Cook Spain, F.A.C.P., New York, N. Y., May 12, 1956
- Dr. Fred Leland Webb, F.A.C.P., Nashville, Tenn., March 26, 1956

The College Headquarters at 4200 Pine Street, Philadelphia 4, Pa., would appreciate it if members and readers sent in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. LYELL CARY KINNEY

Dr. Lyell Cary Kinney, F.A.C.P., died February 1, 1956, in an automobile accident, at Del Mar, California. Bereavement for this distinguished physician who was in his seventy-second year is far-reaching, for his devotion to his fellow servants manifested itself abundantly in diverse community activities and organizational pursuits within his profession. American medicine has suffered a tragic loss in Dr. Kinney's passing.

Dr. Kinney was born at Johnstown, Wisconsin, in 1884, and came to Los Angeles in his early years. He received the degrees of Bachelor of Science from the University of Chicago, in 1905, and Doctor of Medicine from the University of Pennsylvania School of Medicine in 1908. Following an internship of more than two years at the German Hospital (Philadelphia), and a residency in surgery, he returned to Los Angeles as Radiologist for the Moore-White-Moore Clinic, and the California-Lutheran Hospital, and became a member of the faculty of the University of Southern California.

In 1915, Dr. Kinney moved to San Diego, where he established his permanent residence and was the only Radiologist in that area. After his service with the U. S. Navy Medical Corps during World War I, he retired with the rank of Commander.

He was a member of the San Diego County Medical Society; California State Medical Society; American Medical Association; American Roentgen Ray Society; Radiological Society of North America; Pacific Coast Roentgen Ray Society; American College of Radiology; American Cancer Society. He was a Founder and Diplomate of the American Board of Radiology and became a Fellow (1928), and Life Member (1944), of the American College of Physicians.

He held the office of President in various organizations: San Diego County Medical Association (1920); California Medical Association (1930); American Roentgen Ray Society (1944). He was largely instrumental in the formation of the California Medical Association's Cancer Commission (1931), and served for several years as a member of that organization. In 1954, for his faithful service as a Director of the American Cancer Society, he was honored with a plaque.

Dr. Kinney's friends and colleagues paid lasting tribute to his memory and proffered sympathy to his wife, Mrs. Mila J. Kinney, who resides at 18011 Sunburst St., Northridge, California, and his four children, Mrs. Edith M. Lashley, Miss Margery Kinney, Dwight F. Kinney and Lyell Cary Kinney, Jr.

GEORGE C. GRIFFITH, M.D., F.A.C.P., A.C.P. Governor for Southern California

DR. GEORGE STIRLING LANDON

Dr. G. Stirling Landon, F.A.C.P., a beloved pioneer physician of San Bernardino, Calif., died on May 21, 1956, at Sussex, England, after a long illness. Dr. Landon was born in Brazil in 1874, and moved to New York with his parents when he was four years of age. He returned with them to their native England at the age of fourteen. After receiving his schooling in England, he operated a tea plantation in Ceylon, India. It was there that his interest in medicine was aroused by the illnesses which he observed among the native workers. He returned to England where he obtained his medical degrees of M.B., Ch.B. and M.D. (1909), from the University of Edinburgh. He then studied Obstetrics at Dublin, Ireland.

Dr. Landon first set up practice at San Bernardino in 1910, and later moved to Australia. During the first World War, he entered the Australian Army and served for five years in France, Belgium, Italy and Germany. After completion of his military service, he did extensive traveling throughout the world, and in 1920, returned to San Bernardino where he practiced medicine until his retirement in 1950.

He was highly regarded by the medical profession, and for many years was Head of the Medical Service of the County Charity Hospital, and City Health Officer. His voluminous medical library was always at the disposal of his colleagues and his advice was often sought.

He was a member of the San Bernardino County Medical Society, California Medical Association, the American Medical Association, and became a Fellow (1925), of the American College of Physicians.

Dr. Landon made a lasting mark upon the professional and cultural life of San Bernardino, where, besides medical practice, he was best known for his horticultural interest. His garden was a showplace of rare plants and trees that experts thought could not be grown there. Upon retirement in 1950, Dr. Landon left San Bernardino to make his home with his brother in Monnington, Mayfield, Sussex, England, where he resided until his passing.

GEORGE C. GRIFFITH, M.D., F.A.C.P., A.C.P. Governor for Southern California

DR. JAMES ROSS MOORE

Dr. James Ross Moore, F.A.C.P., died of acute myocardial infarction and arteriosclerosis, on February 3, 1956, at Los Angeles, at the age of 82. Dr. Moore was born at Girard, Pa., December 29, 1873. He attended Wabash College (Crawfordsville, Ind.), where he received his B.A. in 1896, and then attended Western Reserve University School of Medicine (Cleveland, Ohio), receiving his M.D. in 1900.

He pursued postgraduate studies at Queen's Square Hospital at London, England, after which he returned to the United States. Dr. Moore became well known as a Consulting Neurologist at the Los Angeles County General Hospital, Director of the Hollywood Hospital, and Senior Neuropsychiatrist at the Hollywood-Presbyterian Hospital. His verve for constructive activity led to his appointment as Trustee at the Patton State Hospital. Dr. Moore was a prolific writer in the field of psychiatry and many of his papers were published in leading medical journals.

He was a member of the Los Angeles County Medical Association; California Medical Association; American Medical Association; Los Angeles Clinical and Pathological Society; Los Angeles Neurological Society; and a Fellow (1917), of the American College of Physicians.

His many friends and colleagues deeply regret his passing and extend their sympathy to his widow, Mrs. Zola B. Moore, who resides at 523 S. Lucerne Blvd., Los Angeles 5, California.

George C. Griffith, M.D., F.A.C.P., A.C.P. Governor for Southern California

DR. DANIEL WESTON ZAHN

Dr. Daniel Weston Zahn, F.A.C.P., died May 6, 1956, at Seattle, of cerebral thrombosis complicating a recent coronary thrombosis. He was born at Brooklyn, N. Y., May 2, 1911. He received his degrees of B.S. (1934), and M.D. (1938), from the University of Glasgow. Dr. Zahn took postgraduate training at New York University-Bellevue Medical Center, University of Washington and Beth-El Hospital, (Brooklyn).

He was Assistant in Medicine at Columbia University College of Physicians and Surgeons, and at the University of Colorado School of Medicine. He was Instructor in Medicine at the University of Washington School of Medicine and later became Clinical Assistant Professor, a post he held until the time of his death.

Dr. Zahn served in the Medical Corps of the U. S. Army, from 1944-47, and was discharged with the rank of Captain. From 1947-48, he was Chief of the Tuberculosis Service at the Veterans Administration Hospital (Fort Logan, Colo.), and in 1948, he joined the Medical Staff of Firland Sanatorium (Seattle), where he became the Chief of Staff in 1954.

Dr. Zahn was a member of the King County Medical Society; Washington State Medical Society; American Medical Association; American Trudeau Society; Pacific Northwest Trudeau Society; Seattle Academy of Internal Medicine; Denver Sanatorium Association; New York State Medical Society; Western Tuberculosis Conference; Western Society for Clinical Research; Diplomate, American Board of Internal Medicine; and Fellow (1951), of the American College of Physicians. Dr. Zahn served as President of the Western Tuberculosis Conference; Pacific Northwest Trudeau Society; and of the Chest X-ray Survey, Inc.

Dr. Zahn did extensive writing during his medical career and contributed many articles in connection with his work in prevention and treatment of tuberculosis, to leading medical journals.

The early and unexpected death of Dr. Zahn is deeply regretted by all his friends and colleagues. He is survived by his widow, Mrs. Charlotte P. Zahn, a daughter, Marcia, and a son, Geoffrey, who reside at 12542 Densmore Ave., Seattle 33, Washington.

James W. Haviland, M.D., F.A.C.P., A.C.P. Governor for Washington

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*Schwartz, E.: New York J. Med. 56:570, 1956.



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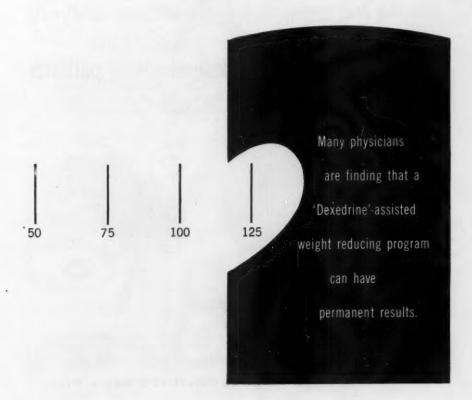
1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).

2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).

3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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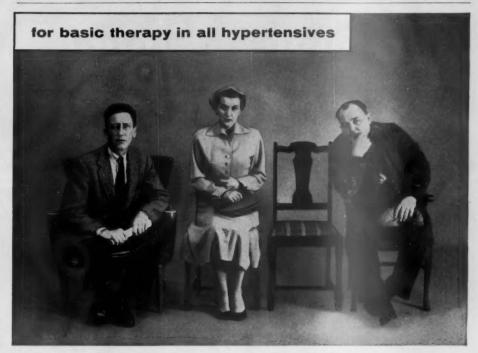
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^{*}Spiesman, M. G., and Malow, L.: New Fecal Softener (Doxinate) in the Treatment of Constipation, Journal-Lancet 76:164 (June) 1956.

^{*}Antos, R. J.: A New Approach to the Treatment of Severe Constipation, Southwestern Med. 37:236 (April) 1956.



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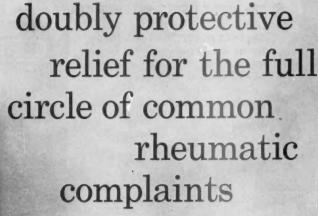
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- 2. Wilkins, R. W.: J. Chronic Dis. 1:563 (May) 1955.
- 3. Moyer, J. H.: Texas J. Med. 51:693 (Oct.) 1955.

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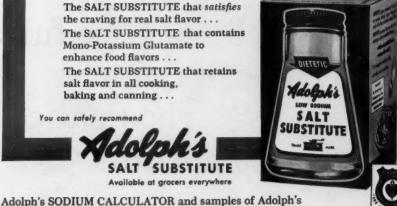
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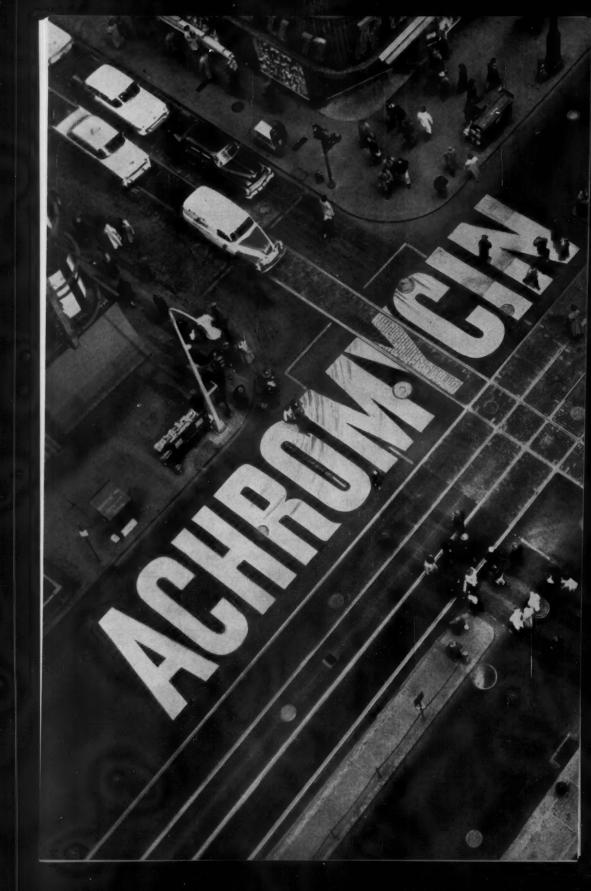
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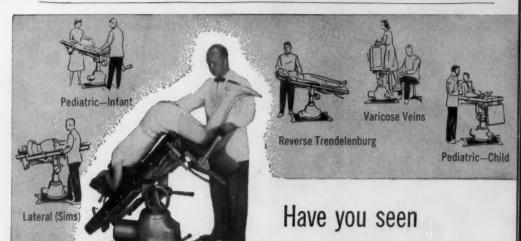
¹Posner, A. C., et al.; Further Observations on the Use of Tetracycline Hydrochloride in Prophylaxis and Treatment of Obstetric Infections, Antibiotics Annual 1954-55, pp. 594-598.

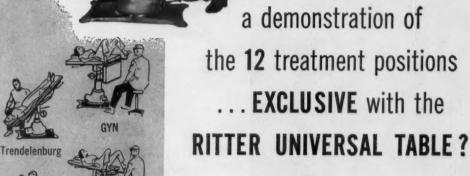


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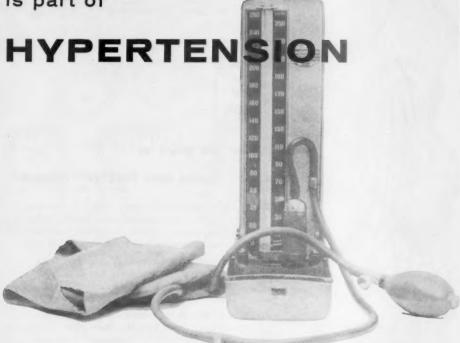
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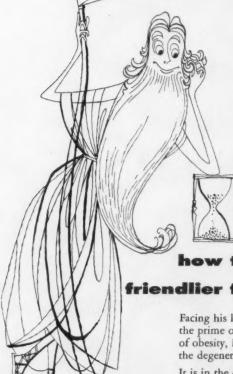
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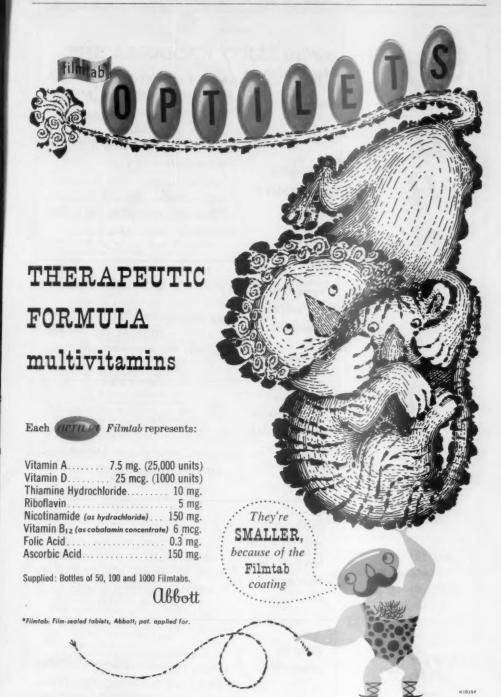
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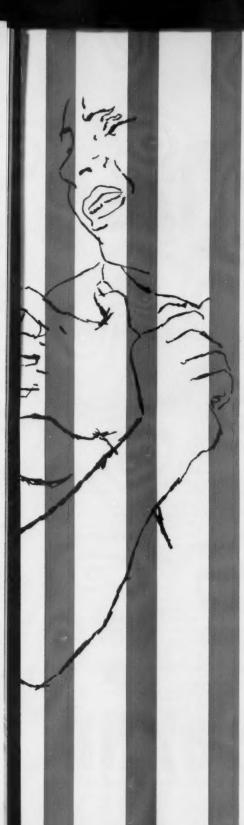
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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

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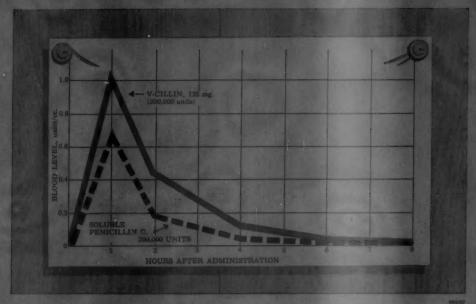
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